A COMPARATIVE STUDY ON THE EFFICACY OF INHALER FORMULATION OF FLUTICASONE PROPIONATE WITH BUDESONIDE AND BECLOMETHASONE DIPROPIONATE IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Dissertation submitted in partial fulfillment of the
Requirement for the award of the degree of

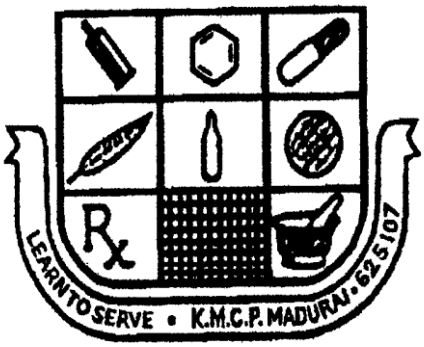
MASTER OF PHARMACY IN

PHARMACYPRACTICE

OF

THE TAMILNADU Dr.M.G.R.MEDICAL UNIVERSITY,

CHENNAI



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APRIL 2016

CERTIFICATE

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It is a bonafide work carried out by him under my guidance and supervision during the academic year **APRIL-2016.** The dissertation partially or fully has not been submitted for any other degree or diploma of this university or other universities.

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ACKNOWLEDGEMENT

In the presentation of this report I recall with sincere gratitude of each of those who have been a source of immense help and inspiration during the progress of report.

I owe my great debt of gratitude to **Mr. M.Nagarajan, M.Pharm., M.B.A., D.M.S.(BM)., D.M.S(IM).**, Correspondent, K. M. College of Pharmacy, for the help and encouraagement rendered to me for the successful completion of this project work and providing all the facilities enabling me to do the work of this magnitude.

It is my privilege to extend my deep sense of thanks to **Dr. S. Venkataraman, M.Pharm., Ph.D., Principal,** K.M. College of pharmacy, for his valuable suggestions and help offered.

It is my privilege to extend my deep sense of thanks to **DR. S.Chidambaranathan, M.Pharm., Ph.D., Vice Principal,** K.M. College of pharmacy, for his valuable suggestions and help offered.

It would be my pleasure to put on record my sincere thanks to **Mr. K. Thirupathi M.Pharm., Head of the Department (Pharmacy Practice),** , for his excellent guidance, help and keen interest during the work.

I express my deep heartfelt and sincere thanks to **Dr.M.Faruk M.B.B.S.,DAC.,D.C.H** Rasi clinic, Ramanathapuram, for his help and encouragement. I admire his systematic and innovative approach and will remain as an ideal symbol of inspiration to me throughout my life.

I owe my warmest and humble thanks to **Mrs. K. Jeyasundari, M.Pharm Asst. Professor** of the department of Pharmacy Practice for her valuable suggestions in completing this work.

A word of special thanks to **Mrs.S. Shanthi** Librarian for kind co-operation in my dissertation work.

Words are inadequate to express my deep sense of gratitude to my lovable colleagues especially **Mr.Lingam,M.Pharm, Mr.Ramanathan,M.Pharm,**

Mr.Anand,M.Pharm, Mr.Sheik,M.Pharm., and all my class mates for their valuable support in giving me the sprit and co-ordination throughout, for the final completion of this thesis work.

I am very much indebted to **my parent's and brother's** for being my guiding spirit and whose blessing and love given me the strength and inspiration to complete this work.

I might have forgotten to name a few people, behind this work, but still really thank all concerned individuals for their support to complete this work successfully in time.

Above all, I proclaim the over whelming presence of the Almighty, who is the source of all wisdom and knowledge for the successful completion of this project work.

V MANIMARAN

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ABBREVIATIONS

COPD	**:**	**Chronic obstructive pulmonary disease**
CDC	**:**	**Centers for Disease Control and Prevention**
NICE	**:**	**National Institute for Health and Clinical Excellence**
CSC	**:**	**Central serous chorioretinopathy**
FEV_1	**:**	**Forced expiratory volume**
FP	**:**	**Fluticasone propionate**
BUD	**:**	**Budesonide**
PFT	**:**	**Pulmonary function test**
ADR	**:**	**Adverse drug reaction**
LABA	**:**	**Long acting Beta agonist**

INTRODUCTION

Chronic obstructive pulmonary disease (COPD)[4] is a respiratory disease characterized by chronic airway inflammation, a decline in lung function over time, and progressive impairment in quality of life. The disease has relatively high prevalence rates worldwide (5–13%) and is mainly caused not only by the inhalation of noxious substances, predominantly cigarette smoking in the Western world, but also by indoor air pollution, particularly in the developing countries. COPD is associated with high mortality and morbidity rates and a high economic and social burden, mainly due to the requirement for substantial and ongoing medical support. COPD is the fourth leading cause of death worldwide and is expected to be the third leading cause by 2030. It is generally believed that despite the availability of both national and international guidelines, COPD remains substantially underdiagnosed and undertreated and is rarely regarded as a health issue of top priority.

For many years, smoking cessation has been known to be the single effective intervention for reducing the risk of developing COPD and slowing its progression down .However, recent data from long-term trials have shown that initiating maintenance pharmacological treatment at early stages of the disease, when there is an opportunity to alter the progression of the disease and maximize patient benefit, may alter the clinical course of COPD and can be more effective than at later stages of the disease . Moreover, it has been demonstrated that despite the relative steroid insensitivity of airway inflammation in COPD, the combination of long-acting bronchodilator therapy with inhaled glucocorticosteroids (ICS)is beneficial for patients with severe COPD . Thus, early and optimal pharmacotherapy appears to be fundamental in the management of COPD

RESPIRATORY DISEASE

Respiratory disease is a medical term that encompasses pathological conditions affecting the organs and tissues that make gas exchange possible in higher organisms, and includes conditions of the upper respiratory tract, trachea, bronchi, bronchioles, alveoli, pleura and pleural cavity, and the nerves and muscles of breathing.

Respiratory diseases range from mild and self-limiting, such as the common cold, to life-threatening entities like bacterial pneumonia, pulmonary embolism, and lung cancer. In humans the anatomical features of the respiratory system include airways, lungs, and the respiratory muscles. Molecules of oxygen and carbon dioxide are passively exchanged, by diffusion, between the gaseous external environment and the blood. This exchange process occurs in the alveolar region of the lungs.

The respiratory system can be subdivided into an upper respiratory tract and a lower respiratory tract based on anatomical features. The upper respiratory tract includes the nasal passages, pharynx and the larynx, while the lower respiratory tract is comprised of the trachea, the primary bronchi and lungs.

The primary function of the respiratory system is to supply the blood with oxygen in order for the blood to deliver oxygen to all parts of the body. The respiratory system does this through breathing. When we breathe, we inhale oxygen and exhale carbon dioxide. This exchange of gases is the respiratory system's means of getting oxygen to the blood. The respiratory system lies dormant in the human fetus during pregnancy. At birth, the respiratory system becomes fully functional upon exposure to air, although some lung development and growth continues throughout childhood. Pre-term birth can lead to infants with under-developed lungs. Smoking and air pollution are two common causes of respiratory problems.

Disorders of the respiratory system can be classified into four general areas:

- Obstructive conditions (e.g., emphysema, bronchitis, asthma attacks)
- Restrictive conditions (e.g., fibrosis, sarcoidosis, alveolar damage, pleural effusion)
- Vascular diseases (e.g., pulmonary edema, pulmonary embolism, pulmonary hypertension)
- Infectious, environmental and other "diseases" (e.g., pneumonia, tuberculosis, asbestosis, particulate pollutants): Coughing is of major importance, as it is the body's main method to remove dust, mucus, saliva, and other debris from the lungs. Inability to cough can lead to infection. Deep breathing exercises may help keep finer structures of the lungs clear from particulate matter, etc.

The respiratory tract is constantly exposed to microbes due to the extensive surface area, which is why the respiratory system includes many mechanisms to defend itself and prevent pathogens from entering the body.

Common Respiratory Disorders Include [51]:

- **Chronic Obstructive Pulmonary Disease (COPD)** - Irritation of the lungs can lead to asthma, emphysema, and chronic bronchitis and people can develop two or three of these together.
- **Chronic Bronchitis** - Any irritant reaching the bronchi and bronchioles will stimulate an increased secretion of mucus. In chronic bronchitis the air passages become clogged with mucus, and this leads to a persistent cough.
- **Emphysema** - The delicate walls of the alveoli break down, reducing the gas exchange area of the lungs. The condition develops slowly and is seldom a direct cause of death.

- **Asthma** - Periodic constriction of the bronchi and bronchioles makes it more difficult to breathe.
- **Pneumonia** - An infection of the alveoli. It can be caused by many kinds of both bacteria and viruses. Tissue fluids accumulate in the alveoli reducing the surface area exposed to air. If enough alveoli are affected, the patient may need supplemental oxygen.
- Disorders of the respiratory system are usually treated internally by a pulmonologist or respiratory physician.

Facts: Respiratory Disorder[52]

- According to the WHO Global Status Report on NCDs 2010, smoking is estimated to cause about 71% of all lung cancer deaths and 42% of chronic respiratory disease worldwide. Of the six WHO regions, the highest overall prevalence for smoking in 2008 was estimated to be the in the European Region, at nearly 29%.
- According to the Centers for Disease Control and Prevention (CDC), COPD is the fourth leading cause of death in the United States. Its prevalence increases with age. Men are more likely to have the disease, but the death rate for men and women is about the same.
- Diseases of the lung and airways are the most common cause of illness in children in developed countries and a leading cause of death in children in developing areas.
- In developed countries the frequency of life threatening acute respiratory infections has dropped over the last 50 years. This is probably due to improved living conditions and health care. Within Europe, there tends to be more asthma and allergy in the West and more infectious diseases in the East.

Chronic obstructive pulmonary disease (COPD)

It is a type of obstructive lung disease characterized by chronically poor airflow. It typically worsens over time. The main symptoms include shortness of breath, cough, and sputum production.[1] Most people with **chronic bronchitis** have COPD.[2]

Tobacco smoking is the most common cause of COPD, with a number of other factors such as air pollution and genetics playing a smaller role.[3] In the developing world, one of the common sources of air pollution is poorly vented cooking and heating fires. Long-term exposure to these irritants causes an inflammatory response in the lungs resulting in narrowing of the small airways and breakdown of lung tissue, known as **emphysema**.[4] The diagnosis is based on poor airflow as measured by lung function tests.[5] In contrast to asthma, the airflow reduction does not improve significantly with the administration of a bronchodilator.

COPD can be prevented by reducing exposure to known environmental risk factors. This includes decreasing rates of smoking and improving indoor and outdoor air quality. COPD treatments include stopping smoking, vaccinations, rehabilitation, and often inhaled bronchodilators and steroids. Some people may benefit from long-term oxygen therapy or lung transplantation. In those who have periods of acute worsening, increased use of medications and hospitalization may be needed.

Worldwide, COPD affects 329 million people or nearly 5 percent of the population.[6] In 2013, it resulted in 2.9 million deaths, up from 2.4 million deaths in 1990.[7] The number of deaths is projected to increase because of higher smoking rates and an aging population in many countries.[8] It resulted in an estimated economic cost of $2.1 trillion in 2010.[9]

COPD classification

All guidelines for the management of COPD have provided with the table below illustrates the gradation of severity as defined by the present guidelines according to airflow obstruction:

		ATS/ERS (2004)[1]	GOLD (2008)[2]	NICE (2010)[3]
Post-bronchodilator FEV1/FVC	**FEV1 predicted**	**Severity of airflow obstruction post-bronchodilator**		
< 70%	≥ 80%	Mild	Stage 1 - Mild	Stage 1 - Mild
< 70%	50 – 79%	Moderate	Stage 2 - Moderate	Stage 2 - Moderate
< 70%	30 – 49%	Severe	Stage 3 - Severe	Stage 3 - Severe
< 70%	< 30%	Very severe	Stage 4 - Very Severe*	Stage 4 - Very severe*

Table: 1 Types of COPD

ATS, American Thoracic Society; ERS, European Respiratory Society; * or FEV1 < 50% with respiratory failure

Sign and symptoms

The most common symptoms of COPD[53] are sputum production, shortness of breath, and a productive cough.[10] These symptoms are present for a prolonged period of time and typically worsen over time. It is unclear if different types of COPD exist. While previously divided into emphysema and chronic bronchitis, emphysema is only a description of lung changes rather than a disease itself, and chronic bronchitis is simply a descriptor of symptoms that may or may not occur with COPD.

Cough

A chronic cough is often the first symptom to develop. When it persists for more than three months each year for at least two years, in combination with sputum production and without another explanation, there is by definition chronic bronchitis. This condition can occur before COPD fully develops. The amount of sputum produced can change over hours to days. In some cases, the cough may not be present or may only occur occasionally and may not be productive. Some people with COPD attribute the symptoms to a "smoker's cough". Sputum may be swallowed or spat out, depending often on social and cultural factors. Vigorous coughing may lead to rib fractures or a brief loss of consciousness. Those with COPD often have a history of "common colds" that last a long time.

Shortness of breath[54]

Shortness of breath is often the symptom that most bothers people. Typically the shortness of breath is worse on exertion of a prolonged duration and worsens over time. In the advanced stages, it occurs during rest and may be always present.[13][14] It is a source of both anxiety and a poor quality of life in those with COPD. Many people with more advanced COPD breathe through pursed lips and this action can improve shortness of breath in some patients.[15][16]

Other features

In COPD[55], it may take longer to breathe out than to breathe in.[17] Chest tightness may occur but is not common and may be caused by another problem. Those with obstructed airflow may have wheezing or decreased sounds with air entry on examination of the chest with a stethoscope. A barrel chest is a characteristic sign of

COPD, but is relatively uncommon. Tripod positioning may occur as the disease worsens.

Advanced COPD leads to high pressure on the lung arteries, which strains the right ventricle of the heart. [18][19] This situation is referred to as corpulmonale, and leads to symptoms of leg swelling and bulging neck veins. COPD is more common than any other lung disease as a cause of corpulmonale. Corpulmonale has become less common since with the use of supplemental oxygen.

COPD often occurs along with a number of other conditions, due in part to shared risk factors. These conditions include ischemic heart disease, high blood pressure, diabetes mellitus, muscle wasting, osteoporosis, lung cancer, anxiety disorder and depression. In those with severe disease, a feeling of always being tired is common. Fingernail clubbing is not specific to COPD and should prompt investigations for an underlying lung cancer.[20]

Exacerbation

An acute exacerbation of COPD[56] is defined as increased shortness of breath, increased sputum production, a change in the color of the sputum from clear to green or yellow, or an increase in cough in someone with COPD. This may present with signs of increased work of breathing such as fast breathing, a fast heart rate,sweating, active use of muscles in the neck, a bluish tinge to the skin, and confusion or combative behavior in very severe exacerbations.[21] Crackles may also be heard over the lungs on examination with a stethoscope.

Cause

The primary cause of COPD[57] is tobacco smoke, with occupational exposure and pollution from indoor fires being significant causes in some countries.[1] Typically

these exposures must occur over several decades before symptoms develop.[1] A person's genetic makeup also affects the risk.[1]

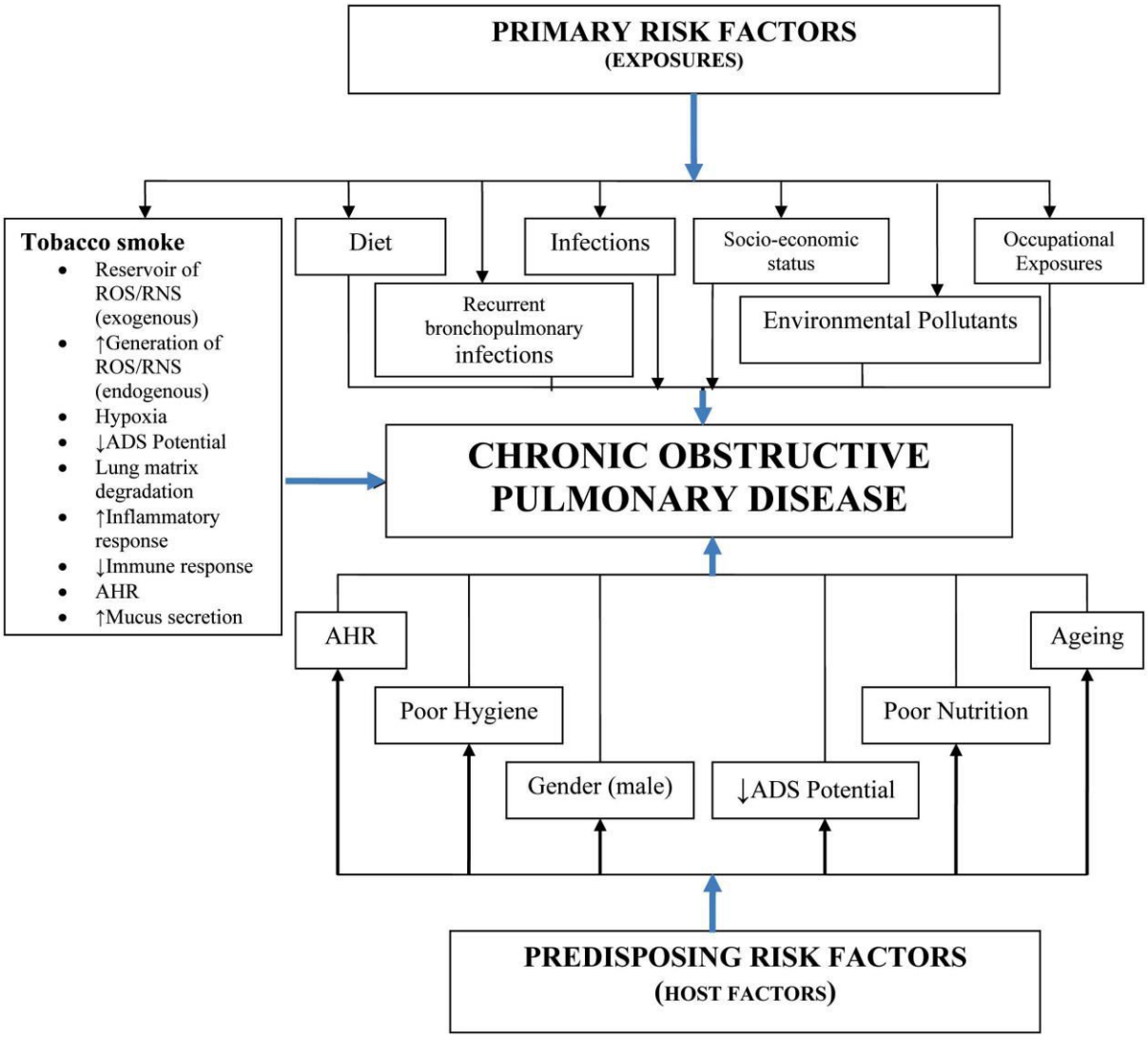

Figure: 1 Primary risk factors

Pathophysiology

COPD[58] develops as a significant and chronic inflammatory response to inhaled irritants. Chronic bacterial infections may also add to this inflammatory state. The inflammatory cells involved include neutrophil granulocytes and macrophages, two types of white blood cell.

Those who smoke additionally have Tc1 lymphocyte involvement and some people with COPD have eosinophil involvement similar to that in asthma. Part of this

cell response is brought on by inflammatory mediators such as chemotactic factors. Other processes involved with lung damage include oxidative stress produced by high concentrations of free radicals in tobacco smoke and released by inflammatory cells, and breakdown of the connective tissue of the lungs by proteases that are insufficiently inhibited by protease inhibitors.

The destruction of the connective tissue of the lungs is what leads to emphysema, which then contributes to the poor airflow and, finally, poor absorption and release of respiratory gases. General muscle wasting that often occurs in COPD may be partly due to inflammatory mediators released by the lungs into the blood.

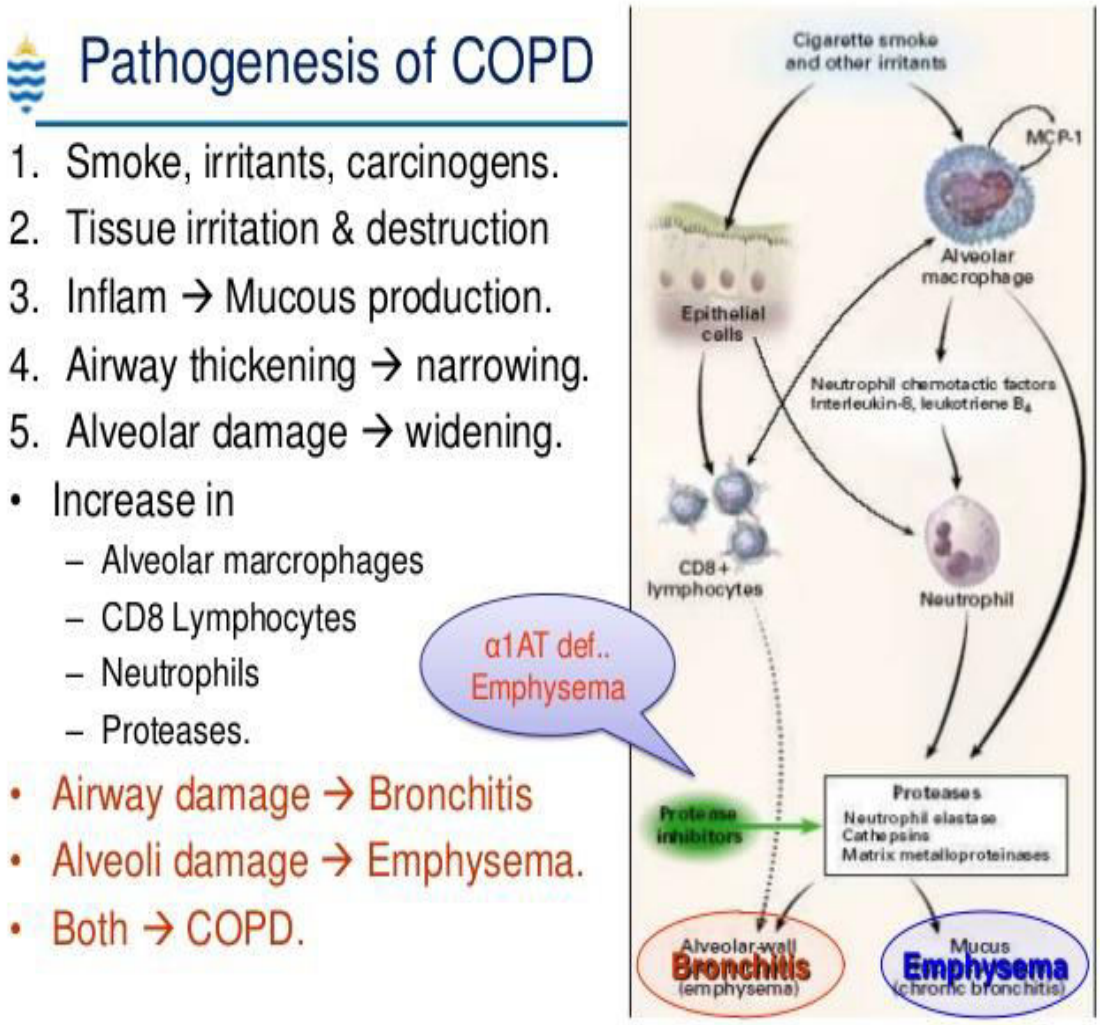

Figure :2 Pathogenesis of COPD

Narrowing of the airways occurs due to inflammation and scarring within them. This contributes to the inability to breathe out fully. The greatest reduction in air flow occurs when breathing out, as the pressure in the chest is compressing the airways at this time. This can result in more air from the previous breath remaining within the lungs when the next breath is started, resulting in an increase in the total volume of air in the lungs at any given time, a process called hyperinflation or air trapping. Hyperinflation from exercise is linked to shortness of breath in COPD[59], as it is less comfortable to breathe in when the lungs are already partly full. Hyperinflation may also worsen during an exacerbation.

Some also have a degree of airway hyper responsiveness to irritants similar to those found in asthma. Low oxygen levels and, eventually, high carbon dioxide levels in the blood can occur from poor gas exchange due to decreased ventilation from airway obstruction, hyperinflation and a reduced desire to breathe. During exacerbations, airway inflammation is also increased, resulting in increased hyperinflation, reduced expiratory airflow and worsening of gas transfer. This can also lead to insufficient ventilation and, eventually, low blood oxygen levels. Low oxygen levels, if present for a prolonged period, can result in narrowing of the arteries in the lungs, while emphysema leads to breakdown of capillaries in the lungs. Both these changes result in increased blood pressure in the pulmonary arteries, which may cause corpulmonale.

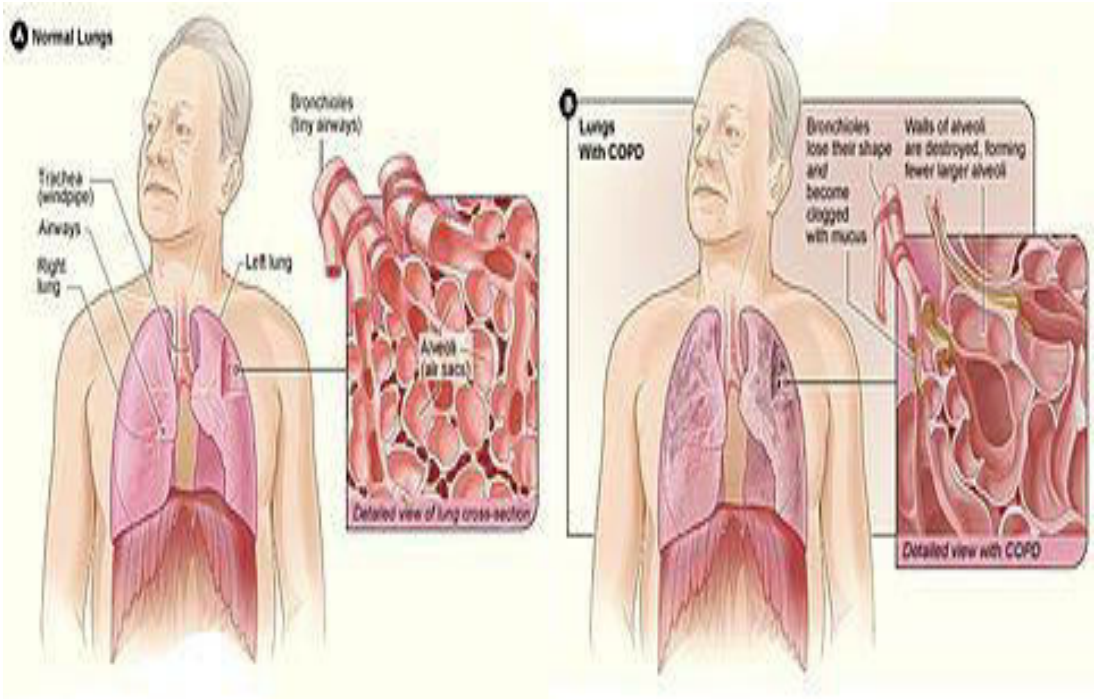

Figure :3 Lungs affected COPD

Diagnosis

The diagnosis of COPD should be considered in anyone over the age of 35 to 40 who has shortness of breath, a chronic cough, sputum production, or frequent winter colds and a history of exposure to risk factors for the disease. Spirometry is then used to confirm the diagnosis.

Differential diagnosis

COPD[60] may need to be differentiated from other causes of shortness of breath such as congestive heart failure, pulmonary embolism, pneumonia or pneumothorax. Many people with COPD mistakenly think they have asthma. The distinction between asthma and COPD is made on the basis of the symptoms, smoking history, and whether airflow limitation is reversible with bronchodilators at spirometry. Tuberculosis may also present with a chronic cough and should be considered in locations where it is common. Less common conditions that may

present similarly include bronchopulmonary dysplasia and obliterative bronchiolitis. Chronic bronchitis may occur with normal airflow.

Prevention

Most cases of COPD[61] are potentially preventable through decreasing exposure to smoke and improving air quality. Annual influenza vaccinations in those with COPD reduce exacerbations, hospitalizations and death. Pneumococcal vaccination may also be beneficial.

Management

There is no known cure for COPD[62], but the symptoms are treatable and its progression can be delayed. The major goals of management are to reduce risk factors, manage stable COPD, prevent and treat acute exacerbations, and manage associated illnesses. The only measures that have been shown to reduce mortality are smoking cessation and supplemental oxygen. Stopping smoking decreases the risk of death by 18%. Other recommendations include influenza vaccination once a year, pneumococcal vaccination once every 5 years, and reduction in exposure to environmental air pollution. In those with advanced disease, palliative care may reduce symptoms, with morphine improving the feelings of shortness of breath. Noninvasive ventilation may be used to support breathing.

Management of COPD

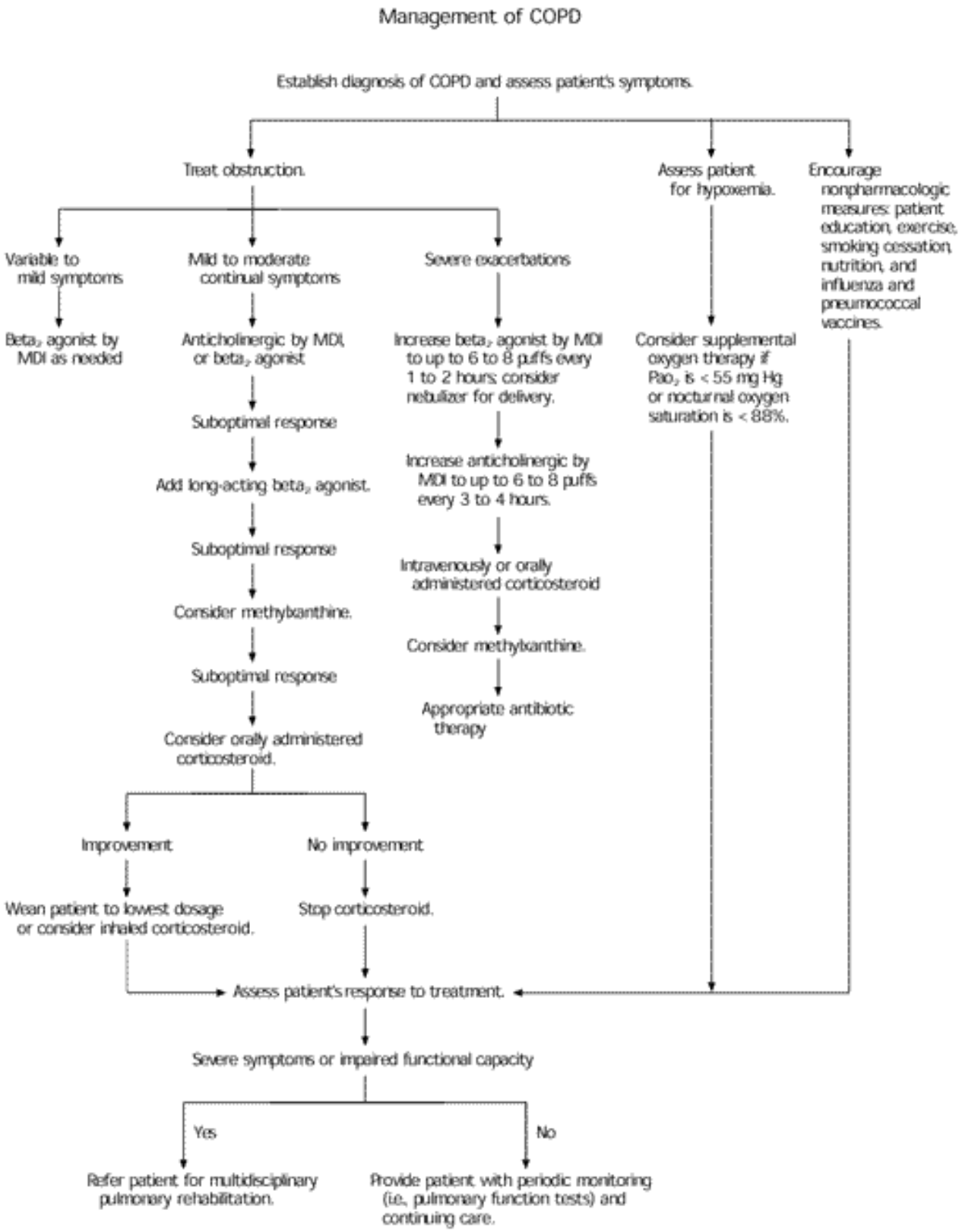

Figure : 4 Management of COPD

Exercise

Pulmonary rehabilitation is a program of exercise, disease management and counseling, coordinated to benefit the individual. In those who have had a recent exacerbation, pulmonary rehabilitation appears to improve the overall quality of life and the ability to exercise, and reduce mortality. It has also been shown to improve the sense of control a person has over their disease, as well as their emotions. Breathing exercises in and of themselves appear to have a limited role. Pursed lip breathing exercises may be useful.

Being either underweight or overweight can affect the symptoms, degree of disability and prognosis of COPD[63]. People with COPD who are underweight can improve their breathing muscle strength by increasing their calorie intake. When combined with regular exercise or a pulmonary rehabilitation program, this can lead to improvements in COPD symptoms. Supplemental nutrition may be useful in those who are malnourished.

Bronchodilators

Inhaled bronchodilators[64] are the primary medications used and result in a small overall benefit. There are two major types, β_2 agonists and anticholinergics; both exist in long-acting and short-acting forms. They reduce shortness of breath, wheeze and exercise limitation, resulting in an improved quality of life. It is unclear if they change the progression of the underlying disease.

In those with mild disease, short-acting agents are recommended on an as needed basis. In those with more severe disease, long-acting agents are recommended. Long acting agents partly work by improving hyperinflation. If long-acting bronchodilators are insufficient, then inhaled corticosteroids are typically added. With respect to long-acting agents, it is unclear if Ipratropium (a long-acting

anticholinergic) or long-acting beta agonists (LABAs) are better, Both types of agent appear to reduce the risk of acute exacerbations by 15–25%. While both may be used at the same time, any benefit is of questionable significance.

There are several short-acting β2 agonists available including salbutamol (Ventolin) and terbutaline They provide some relief of symptoms for four to six hours. Long-acting β2 agonists such as salmeterol and formoterol are often used as maintenance therapy. Some feel the evidence of benefits is limited while others view the evidence of benefit as established. Long-term use appears safe in COPD[65] with adverse effects include shakiness and heart palpitations. When used with inhaled steroids they increase the risk of pneumonia. While steroids and LABAs may work better together, it is unclear if this slight benefit outweighs the increased risks.

There are two main anticholinergics used in COPD, ipratropium and tiotropium. Ipratropium is a short-acting agent while tiotropium is long-acting. Tiotropium is associated with a decrease in exacerbations and improved quality of life, and tiotropium provides those benefits better than ipratropium. It does not appear to affect mortality or the overall hospitalization rate. Anticholinergics can cause dry mouth and urinary tract symptoms. They are also associated with increased risk of heart disease and stroke. Aclidinium, another long acting agent which came to market in 2012, has been used as an alternative to tiotropium.

Corticosteroids

Corticosteroids are usually used in inhaled form but may also be used as tablets to treat and prevent acute exacerbations. While inhaled corticosteroids (ICS) have not shown benefit for people with mild COPD[66], they decrease acute exacerbations in those with either moderate or severe disease. When used in combination with a LABA[67] they decrease mortality more than either ICS or LABA

alone. By themselves they have no effect on overall one-year mortality and are associated with increased rates of pneumonia. It is unclear if they affect the progression of the disease. Long-term treatment with steroid tablets is associated with significant side effects.

Other medication

Long-term antibiotics, specifically those from the macrolide class such as erythromycin, reduce the frequency of exacerbations in those who have two or more a year. This practice may be cost effective in some areas of the world. Concerns include that of antibiotic resistance and hearing problems with azithromycin. Methylxanthines such as theophylline generally cause more harm than benefit and thus are usually not recommended, but may be used as a second-line agent in those not controlled by other measures. Mucolytics may help to reduce exacerbations in some people with chronic bronchitis. Cough medicines are not recommended.

Oxygen

Supplemental oxygen is recommended in those with low oxygen levels at rest . In this group of people it decreases the risk of heart failure and death if used 15 hours per day and may improve people's ability to exercise. In those with normal or mildly low oxygen levels, oxygen supplementation may improve shortness of breath. There is a risk of fires and little benefit when those on oxygen continue to smoke. In this situation some recommend against its use. During acute exacerbations, many require oxygen therapy; the use of high concentrations of oxygen without taking into account a person's oxygen saturations may lead to increased levels of carbon dioxide and worsened outcomes. In those at high risk of high carbon dioxide levels,

oxygen saturations of 88–92% are recommended, while for those without this risk recommended levels are 94–98%.

Surgery

For those with very severe disease, surgery is sometimes helpful and may include lung transplantation or lung volume reduction surgery. Lung volume reduction surgery involves removing the parts of the lung most damaged by emphysema allowing the remaining, relatively good lung to expand and work better. Lung transplantation is sometimes performed for very severe COPD,[68] particularly in younger individuals.

Exacerbations

Acute exacerbations are typically treated by increasing the usage of short-acting bronchodilators. This commonly includes a combination of a short-acting inhaled beta agonist and anticholinergic. These medications can be given either via a metered-dose inhaler with a spacer or via a nebulizer with both appearing to be equally effective. Nebulization may be easier for those who are more unwell.

Oral corticosteroids improve the chance of recovery and decrease the overall duration of symptoms. They work equally well as intravenous steroids but appear to have fewer side effects. Five days of steroids work as well as ten or fourteen. In those with a severe exacerbation, antibiotics improve outcomes. A number of different antibiotics may be used including amoxicillin, doxycycline and azithromycin; it is unclear if one is better than the others. There is no clear evidence for those with less severe cases.

For those with type 2 respiratory failure non-invasive positive pressure ventilation decreases the probability of death or the need of intensive care

admission. Additionally, theophylline may have a role in those who do not respond to other measures. Fewer than 20% of exacerbations require hospital admission. In those without acidosis from respiratory failure, home care may be able to help avoid some admissions.

Corticosteroids

- **Corticosteroids** are a class of steroid hormones that are produced in the adrenal cortex of vertebrates, as well as the synthetic analogues of these hormones. Corticosteroids are involved in a wide range of physiological processes, including stress response, immune response, and regulation of inflammation, carbohydrate metabolism, protein catabolism, blood electrolyte levels, and behavior.

- **Glucocorticoids** such as cortisol control carbohydrate, fat and protein metabolism, and are anti-inflammatory by preventing phospholipid release, decreasing eosinophil action and a number of other mechanisms.[22]
- **Mineralocorticoids** such as aldosterone control electrolyte and water levels, mainly by promoting sodium retention in the kidney.

Medical uses[70]

Synthetic pharmaceutical drugs with corticosteroid-like effects are used in a variety of conditions, ranging from brain tumors to skin diseases. Dexamethasone and its derivatives are almost pure glucocorticoids, while prednisone and its derivatives have some mineralocorticoid action in addition to the glucocorticoid effect. Fludrocortisone (Florinef) is a synthetic mineralocorticoid. Hydrocortisone (cortisol) is available for replacement therapy, e.g. in adrenal insufficiency and congenital adrenal hyperplasia.

Synthetic glucocorticoids are used in the treatment of joint pain or inflammation (arthritis), temporal arteritis, dermatitis, allergic reactions, asthma, hepatitis,systemic lupus erythematosus, inflammatory bowel disease (ulcerative colitis and Crohn's disease), sarcoidosis and for glucocorticoid replacement in Addison's disease or other forms of adrenal insufficiency.[23] Topical formulations are also available for the skin, eyes (uveitis), lungs (asthma), nose (rhinitis), and bowels. Corticosteroids are also used supportively to prevent nausea, often in combination with 5-HT3 antagonists (e.g. ondansetron).

Typical undesired effects of glucocorticoids present quite uniformly as drug-induced Cushing's syndrome. Typical mineralocorticoid side-effects are hypertension(abnormally high blood pressure), hypokalemia (low potassium levels in the blood), hypernatremia (high sodium levels in the blood) without causing peripheral edema, metabolic alkalosis and connective tissue weakness.[24] There may also be impaired wound healing or ulcer formation because of the immunosuppressive effects.

Clinical and experimental evidence indicates that corticosteroids can cause permanent eye damage by inducing central serous retinopathy (CSR, also known as central serous chorioretinopathy, CSC). A variety of steroid medications, from anti-allergy nasal sprays (Nasonex, Flonase) to topical skin creams, to eye drops (Tobradex), to prednisone have been implicated in the development of CSR.[25][26]

Corticosteroids have been widely used in treating people with traumatic brain injury.[27] A systematic review identified 20 randomised controlled trials and included 12,303 participants, then compared patients who received corticosteroids with patients who received no treatment. The authors recommended people with traumatic head injury should not be routinely treated with corticosteroids.[28]

Classification

Chemical structure

In general, corticosteroids are grouped into four classes, based on chemical structure. Allergic reactions to one member of a class typically indicate an intolerance of all members of the class. This is known as the "Coopman classification"[46], after S. Coopman, who defined this classification in 1989.[47].

The highlighted steroids are often used in the screening of allergies to topical steroids. [48]

Group A - Hydrocortisone type

Hydrocortisone, hydrocortisoneacetate, cortisone acetate, tixocortolpivalate, prednisolone, methylprednisolone, and prednisone (Short- to medium-acting glucocorticoids).

Group B - Acetonides (and related substances)

Triamcinolone acetonide, triamcinolone alcohol, mometasone, amcinonide, budesonide, desonide, fluocinonide, fluocinolone acetonide, and halcinonide.

Group C - Betamethasone type

Betamethasone, betamethasone sodium phosphate, dexamethasone, dexamethasone sodium phosphate, and fluocortolone.

Group D - Esters

Group D1 - Halogenated (less labile)

Hydrocortisone-17-alerate, halometasone, alclometasonedipropionate, betamethasone valerate, betamethasone dipropionate, prednicarbate, clobetasone-17-butyrate, clobetasol-17-propionate, fluocortolone caproate, fluocortolonepivalate, and fluprednidene acetate.

Group D2 - Labile prodrug esters

Hydrocortisone-17-butyrate, hydrocortisone-17-aceponate, hydrocortisone-17-buteprate, ciclesonide and prednicarbate.

Route of administration

Topical steroids

For use topically on the skin, eye, and mucous membranes.Topical corticosteroids are divided in potency classes I to IV, Inhaled steroids for use to treat the nasal mucosa, sinuses, bronchii, and lungs.[49] This group includes

- Flunisolide
- Fluticasone furoate
- Fluticasone propionate
- Triamcinolone acetonide
- Beclomethasone dipropionate
- Budesonide

There is also a combination preparation containing fluticasone propionate[50] and salmeterol xinafoate (a long-acting bronchodilator). It is approved for children over 12 years old.

Oral forms

Such as prednisone and prednisolone.

Systemic forms

Available in injectables for intravenous and parenteral routes.

REVIEW OF LITERATURE

James F. Donohue et al.,[79] studied that once-daily UMEC/VI 62.5/25 mcg over 12 weeks resulted in statistically significant, clinically meaningful improvements in lung function versus twice-daily FP/SAL 250/50 mcg in patients with moderate-to-severe COPD with infrequent exacerbations. Both treatments improved dyspnea and QoL.

Yoshihisa Ishiura et al.,[80] studied that the mean values for the FEV1 were 1.33 (±0.29) L in the run-in period, 1.38 (±0.39) L after the FP/SAL treatment period, and 1.47 (±0.38) L after the FF/VI treatment period. The FEV1 value after the FF/VI treatment was significantly greater than the value after the run-in period ($p < 0.01$). The FF/VI treatment period FF/VI, the first once-daily ICS/LABA, can provide substantial improvement in lung functions, indicating that FF/VI should be considered for the regular treatment of ACOS.

Lucia Spicuzza et al.,[81] studied that the subjects with asthma, 1000 μg FP in a single dose significantly attenuated the constrictor response to AMP, geometric mean (range) PC20AMP values increasing from a 19.2 (1.3–116.3) to 81.5 (9.6–1600.0) ($p < 0.001$; post-placebo vs post-FP) mg/ml. Change in the airways response to inhaled AMP after FP was well within test variability in patients with COPD, with PC20AMP values 59.6 (11.3–183.9) and 76.3 (21.0–445.3) ($p = 0.022$; post-placebo vs post-FP) mg/ml. Additionally, FP failed to significantly attenuate the bronchial response to methacholine in both asthma and COPD subjects. A change in doubling dilution, between placebo and following a single dose of FP, in AMP had a better sensitivity and specificity of 95.8% and 65.2%, compared to methacholine of 79.2% and 43.5% respectively in delineating between COPD and asthma.A single dose of 1000 μg FP

rapidly improves AHR to AMP in asthmatics but not in COPD subjects. This may provide a convenient way by which provocation challenge with inhaled AMP may help in discriminating asthma from COPD.

Andre-Bernard Tonnel et al.,[82] studied that the overall response rate to FSC at 6 and 12 weeks was 79%. The corresponding rates for FEV_1, IC, and QoL were 38%, 55%, and 62%, respectively. More than 40% of patients showed a response for IC and/or QoL without being responders for FEV_1.Overall lung function and QoL were improved. FSC was well tolerated with a safety profile consistent with that observed previously.Nearly 80% of patients responded to FSC treatment in this real-life study. Improvements in IC and QoL at 12 weeks revealed a clinically relevant response in patients with no improvement in FEV_1. IC reversibility to salbutamol before treatment might represent, better than FEV1, a prognostic factor of response to FSC in severe COPD. Moreover these tests are easy to perform routinely and in large numbers of patients.

Mario Cazzola et al.,[83] studied that the difference in the onset of bronchodilatation between formoterol/beclomethasone 12/200 μg Modulite and formoterol / budesonide 9/320 μg Turbuhaler in patients with COPD. We enrolled 28 patients with stable COPD. Both formoterol / beclomethasone and formoterol/budesonide elicited a larger mean FEV_1–$AUC_{0–15min}$ than formoterol alone, whereas there was no significant difference between their FEV_1–$AUC_{0–15min}$. Also the change in FEV_1 15 min after inhalation of formoterol/beclomethasone combination or formoterol/budesonide combination was greater than that induced by formoterol alone. This study confirms the rapid effect of the inhaled corticosteroid component when combined with formoterol and indicates that the onset of bronchodilation of

formoterol/beclomethasone Modulite and formoterol/budesonide Turbuhaler are similar and greater than formoterol alone in patients with COPD.

Heinrich Worth et al.,[84] studied that the Budesonide/formoterol resulted in a significant improvement in endurance time 1 h after the last morning dose in a 1-week treatment period versus formoterol and placebo. This study demonstrates, for the first time, the benefit of inhaled corticosteroids in addition to long-acting β_2-agonists on exercise tolerance in COPD patients.

Lucie Blais et al.,[85] studied that the 2262 patients in the matched cohort, 78.1% were aged ≥65 years and 52.1% were men. COPD exacerbations, claims for oral corticosteroids, use of SABAs, and patient adherence to treatment did not differ significantly between the BUD/FM and FP/SM groups. However, the BUD/FM group was significantly less likely to have an ED visit (adjusted relative risk [RR] = 0.75; 95% CI, 0.58 to 0.97) or hospitalization (adjusted RR = 0.61; 95% CI, 0.47 to 0.81) for COPD and had fewer claims for prescriptions for tiotropium (adjusted RR = 0.71; 95% CI, 0.57 to 0.89). The BUD/FM group also used fewer doses of ipratroprium bromide than the FP/SM group (adjusted mean difference, −0.2 dose; 95% CI, −0.3 to -0.1).These COPD patients treated with BUD/FM were less likely to have ED visits and hospitalizations for COPD and used fewer doses of anticholinergic medication than patients treated with FP/SM in the year after treatment initiation. However, due to the observational nature of the study design, we cannot conclude with certainty that the medication was the only factor responsible for the observed differences.

Gene Colice et al. [86] studied that the Patients started on HFA-beclomethasone had significantly higher odds (adjusted odds ratio, 1.19; 95% CI; 1.08-1.31) of achieving

overall control (risk and impairment), which was defined as no hospital attendance for asthma, oral corticosteroids, or antibiotics for lower respiratory tract infection and less than 2 puffs per day of short-acting β-agonist; they also experienced a lower rate of respiratory-related hospitalizations or referrals (adjusted rate ratio, 0.82; 95% CI, 0.73-0.93) than patients started on fluticasone. Other database outcome measures were similar in the 2 cohorts. Prescribed HFA-beclomethasone doses were lower (P < .001) than fluticasone doses (median, 320 μg/d [interquartile range, 160-320 μg/d] vs 440 μg/d [interquartile range, 176-440 μg/d]). Adjusted respiratory-related health care costs were significantly lower for HFA-beclomethasone than fluticasone (mean, $1869 [95% CI, $1727-$2032] vs $2259 [95% CI, $2111-$2404]), representing a mean annual savings of $390 (95% CI, $165-$620) per patient prescribed HFA-beclomethasone rather than fluticasone.Asthma treatment outcomes were similar or better with HFA-beclomethasone prescribed at significantly lower doses and with lower costs than fluticasone.

David Price et al., [87] studied that More than 80% of patients in each population achieved asthma control; 10% and 16% of patients in the initiation and step-up populations, respectively, received add-on or combination therapy during the year. Fluticasone was prescribed at significantly higher doses than HFA-beclomethasone for both populations (P ≤ .001). In the initiation population (n = 1319 in each cohort) the adjusted odds ratio for achieving asthma control with HFA-beclomethasone was 1.30 (95% CI, 1.02-1.65) relative to fluticasone. In the step-up population (cohorts: n = 250) the adjusted odds ratio for achieving asthma control with HFA-beclomethasone was 1.22 (95% CI, 0.66-2.26). Exacerbation rates were similar between cohorts.In a real-world setting patients receiving HFA-beclomethasone had a

similar or better chance of achieving asthma control at lower prescribed doses than with fluticasone.

P.M.A. Calverley et al.,[88] studied that *the* 718 patients randomised, 703 (232 beclomethasone/formoterol, 238 budesonide/formoterol, 233 formoterol) were in the ITT analysis. Improvement in pre-dose morning FEV_1 was 0.077 L, 0.080 L and 0.026 L for beclomethasone/formoterol, budesonide/formoterol and formoterol respectively (LS mean from the ANOVA model). Beclomethasone/formoterol was not inferior to budesonide/formoterol (95% CI of the difference −0.052, 0.048) and superior to formoterol ($p = 0.046$). The overall rate of COPD exacerbations/patient/year was similar and not statistically significantly different among treatments (beclomethasone/formoterol 0.414, budesonide/formoterol 0.423 and formoterol 0.431). Quality of life and COPD symptoms improved in all groups and use of rescue medication decreased. Safety profiles were as expected and treatments well-tolerated.Beclomethasone/formoterol (400/24 μg) treatment for 48 weeks improved pulmonary function, reduced symptoms compared to formoterol, was safe and well-tolerated in patients with severe stable COPD. Neither of the long-acting β2-agonist/inhaled corticosteroid combinations affected the low exacerbation rate seen in this population.

E. Harmanci et al.,[89] studied that the both BUD and FP improved clinical parameters as determined by FEV1 ($p < 0.05$) and PEFR ($p < 0.01$). There was no difference in respect to log PC20 values in either group ($p > 0.05$). Both treatments didn't change morning cortisol ($p < 0.05$). Both FP and BUD didn't change any indices of bone formation as determined by serum alkalin phosphatase, bone alkalin phosphatase, osteocalcin and carboxyterminalpropeptide of type 1 procollagen and

bone resorption as determined by urinary calcium and deoxypyridinoline ($p > 0.05$). ln addition there was no significant effect on calcium and phosphate metabolism (serum calcium, phosphate and parathyroid hormone).As result, having no adverse effect on bone metabolism and adrenal function, in the regard to clinical efficacy, FP is as effective as the double dose of BUD on PEFR and FEV1.

Christian Frois et al.,[90] studied that the systematic review, fluticasone and formoterol appear to provide improved therapeutic benefits versus budesonide and salmeterol, respectively. Both fluticasone/salmeterol and budesonide/ formoterol combination therapies appeared to be associated with greater improvements in outcomes measures than the corresponding ICS and LABA monotherapies.

Gene Colice et al.,[91] studied that the Patients started on HFA-beclomethasone had significantly higher odds (adjusted odds ratio, 1.19; 95% CI; 1.08-1.31) of achieving overall control (risk and impairment), which was defined as no hospital attendance for asthma, oral corticosteroids, or antibiotics for lower respiratory tract infection and less than 2 puffs per day of short-acting β-agonist; they also experienced a lower rate of respiratory-related hospitalizations or referrals (adjusted rate ratio, 0.82; 95% CI, 0.73-0.93) than patients started on fluticasone. Other database outcome measures were similar in the 2 cohorts. Prescribed HFA-beclomethasone doses were lower ($P < .001$) than fluticasone doses (median, 320 μg/d [interquartile range, 160-320 μg/d] vs 440 μg/d [interquartile range, 176-440 μg/d]). Adjusted respiratory-related health care costs were significantly lower for HFA-beclomethasone than fluticasone (mean, $1869 [95% CI, $1727-$2032] vs $2259 [95% CI, $2111-$2404]), representing a mean annual savings of $390 (95% CI, $165-$620) per patient prescribed HFA-beclomethasone rather than fluticasone.Asthma treatment outcomes were similar or

better with HFA-beclomethasone prescribed at significantly lower doses and with lower costs than fluticasone.

Gordon D. Raphael et al.,[92] studied that the Fluticasone propionate treatment resulted in significantly ($P \leq .034$) greater improvements in objective pulmonary function parameters than did beclomethasone dipropionate treatment and significantly greater reductions in daily albuterol use ($P \leq .010$) and asthma symptoms ($P \leq .027$). Both low-dose (88 μg twice daily) and medium-dose (220 μg twice daily) fluticasone propionate significantly increased FEV1 compared with higher doses of beclomethasone dipropionate ($P = .006$). Low-dose and medium-dose fluticasone propionate improved FEV1 by 0.31 L (14%) and 0.36 L (15%), respectively, compared with improvements of 0.18 L (8%) and 0.21 L (9%) with low-dose and medium-dose beclomethasone dipropionate. The adverse event profiles were similar for both medications.Fluticasone propionate provides greater asthma control at roughly half the dose of beclomethasone dipropionate, with a comparable adverse event profile.

Sailakshmi K et al.,[93] studied that the Symptomatic improvement was observed in all three groups. At end point, mean FEV1 in fluticasone propionate treatment group improved by 22.04% compared with 14.53% in budesonide and 12.02% in beclomethasone treatment groups. At end point, mean FVC value of the fluticasone propionate treatment group improved by 8.04% compared with 5.29% in budesonide and 4.27% in beclomethasone groups. Mean FEV1 / FVC also improved by 12.76% in the fluticasone propionate group compared with 8.63 % in budesonide and 7.45 % in beclomethasone groups. No adverse effects were reported in any of the treatment groups. This study showed that fluticasone propionate is superior to budesonide and

beclomethasone in improving lung function, decreasing symptoms and need for rescue medication in mild persistent asthma.

Lindberg A et al.,[94] studied that the Prevalence of chronic obstructive pulmonary disease according to BTS, ERS, GOLD and ATS criteria in relation to doctor's diagnosis, symptoms, age, gender, and smoking habits. To estimate prevalence of COPD using the guidelines of the British Thoracic Society (BTS), the European Respiratory Society (ERS), the Global Initiative for Chronic Obstructive Lung Disease (GOLD), and the American Thoracic Society (ATS). Further, to evaluate reported airway symptoms, contacts with health care providers, and physician diagnosis of COPD in relation to the respective criteria, and gender differences.in 1992 a postal questionnaire was sent to a random sample of adults aged 20-69 years, 4,851 (85%) out of 5,681 subjects responded. In 1994-1995 a random sample of the responders, 970 subjects, were invited to a structured interview and a lung function test; 666 (69%) participated.The prevalence of COPD was 7.6, 14.0, 14.1, 12.2 and 34.1% according to BTS, ERS, GOLD, clinical ATS (with symptoms or physician diagnosis), and spirometric ATS criteria, respectively. Prevalent COPD was related to age, smoking habits and family history of obstructive airway disease but not to gender. Physician diagnosis of chronic bronchitis or emphysema was only reported by 16.3, 12.2, 11.0, 23.4 and 8.2% of subjects fulfilling the respective criteria, though a majority reported airway symptoms.The main determinants for prevalent COPD were age, smoking habits and spirometric criteria of COPD. Though a majority reported airway symptoms and contact with health care providers due to respiratory complaints, only a minority was diagnosed as having COPD, indicating a large underdiagnosis.

Vaz Fragoso CA et al.,[95] studied that the The ratio of FEV1 to FVC as a basis for establishing chronic obstructive pulmonary disease To evaluate the association between the LMS method of determining the LLN for the FEV1/FVC, set at successively higher thresholds, and clinically meaningful outcomes.Using data from a nationally representative sample of 3,502 white Americans aged 40-80 years, we stratified the FEV1/FVC according to the LMS-LLN, with thresholds set at the 5th, 10th, 15th, 20th, and 25th percentiles (i.e., LMS-LLN5, LMS-LLN10, etc.). We then evaluated whether these thresholds were associated with an increased risk of death or prevalence of respiratory symptoms. Spirometry was not specifically completed after a bronchodilator.Relative to an FEV1/FVC greater than or equal to LMS-LLN25 (reference group), the risk of death and the odds of having respiratory symptoms were elevated only in participants who had an FEV1/FVC less than LMS-LLN(5), with an adjusted hazard ratio of 1.68 (95% confidence interval, 1.34-2.12) and an adjusted odds ratio of 2.46 (95% confidence interval, 2.01-3.02), respectively, representing 13.8% of the cohort. Results were similar for persons aged 40-64 years and those aged 65-80 years. In white persons aged 40-80 years, an FEV1/FVC less than LMS-LLN5 identifies persons with an increased risk of death and prevalence of respiratory symptoms. These results support the use of the LMS-LLN5 threshold for establishing chronic obstructive pulmonary disease.

Lundback B et al.,[96] studied tha the Not 15 but 50% of smokers develop COPD?--Report from the Obstructive Lung Disease in Northern Sweden Studies To estimate the prevalence of COPD as defined by British Thoracic Society (BTS) criteria and the recent global initiative for chronic obstructive lung disease (GOLD) criteria. Further aims were to assess the proportion of underdiagnosis and of symptoms in subjects

with COPD, and to study risk factors for COPD.In 1996, 5892 of the Obstructive Lung Disease in Northern Sweden (OLIN) Study's first cohort could be traced to a third follow-up survey, and 5189 completed responses (88%) were received corresponding to 79% of the original cohort from December 1985. Of the responders, a random sample of 1500 subjects were invited to a structured interview and a lung function test, and 1237 of the invited completed a lung function test with acceptable quality.In ages >45 years, the prevalence of COPD according to the BTS guidelines was 8%, while it was 14% according to the GOLD criteria. The absolutely dominating risk factors were increasing age and smoking, and approximately a half of elderly smokers fulfilled the criteria for COPD according to both the BTS and the GOLD criteria. Family history of obstructive airway disease was also a risk factor, while gender was not. Of those fulfilling the BTS criteria for COPD, 94% were symptomatics, 69% had chronic productive cough, but only 31% had prior to the study been diagnosed as having either chronic bronchitis, emphysema, or COPD. The corresponding figures for COPD according GOLD were 88, 51, and 18%.In ages >45 years, the prevalence of COPD according to the BTS guidelines was 8%, and it was 14% according to the GOLD criteria. Fifty percent of elderly smokers had developed COPD. The large majority of subjects having COPD were symptomatic, while the proportion of those diagnosed as having COPD or similar diagnoses was small.

Al-Hazmi M et al.,[97] studied that the Airflow obstruction in young adults Airflow obstruction is relatively uncommon in young adults, and may indicate potential for the development of progressive disease. The objective of the present study was to enumerate and characterize airflow obstruction in a random sample of Canadians aged 20 to 44 years.The sample (n=2962) was drawn from six Canadian sites.A prevalence

study using the European Community Respiratory Health Survey protocol was conducted. Airflow obstruction was assessed by spirometry. Bronchial responsiveness, skin reactivity to allergens and total serum immunoglobulin E were also measured. Logistic regression was used for analysis.Airflow obstruction was observed in 6.4% of the sample, not associated with sex or age. The risk of airflow obstruction increased in patients who had smoked and in patients who had lung trouble during childhood. Adjusted for smoking, the risk of airflow obstruction was elevated for subjects with past and current asthma, skin reactivity to allergens, elevated levels of total immunoglobulin E and bronchial hyper-responsiveness. Of the subjects with airflow obstruction, 21% were smokers with a history of asthma, 50% were smokers without asthma, 12% were nonsmokers with asthma and 17% were nonsmokers with no history of asthma. Bronchial hyper-responsiveness increased the prevalence of airflow obstruction in each of these groups.Smoking and asthma, jointly and individually, are major determinants of obstructive disorders in young adults. Bronchial hyper-responsiveness contributes to obstruction in both groups.

Viegi G.et al.,[98] studied that the The proportional Venn diagram of obstructive lung disease in the Italian general population The Venn diagram of obstructive lung disease (OLD) has been recently quantified. We aimed to quantify the proportion of the general population with OLD, and the intersections of physician-diagnosed asthma, chronic bronchitis (CB), and emphysema in two Italian general population samples, in relationship to airflow obstruction (AO) determined through spirometry.We analyzed data from two prospective studies (4,353 patients) carried out in the rural area of Po River delta from 1988 to 1991 and in the urban area of Pisa from 1991 to 1993.Prevalence rates of asthma, CB, and emphysema were 5.3%, 1.5%, and 1.2% in

the Po delta, and 6.5%, 2.5%, and 3.6% in Pisa. A double Venn diagram, which was used to quantify the distribution of CB, emphysema, and asthma in relation to the presence/absence of AO, identified 15 categories. Isolated AO was the most frequent category (Po delta, 11.0%; Pisa, 6.7%), followed by asthma only without AO (Po delta, 3.3%; Pisa, 4.3%). The combination of the three OLD conditions was the only category that always showed higher prevalence rates for those with AO (Po delta, 0.20%; Pisa, 0.16%) than for those without AO (Po delta, 0.04%; Pisa, 0.05%). Of those with either OLD or AO, there were 61.4% in Po delta and 38.2% in Pisa with isolated AO, 24.8% and 41.9%, respectively, with an OLD without AO, and 13.8% and 19.9%, respectively, with simultaneous OLD and AO. For both genders, the frequency of isolated asthma decreased with age, while that of isolated AO, CB-emphysema, and the combination of asthma and CB-emphysema increased. About 18% of the Italian general population samples either reported the presence of OLD or showed spirometric signs of AO. We confirmed that the Venn diagram of OLD can be quantified in the general population by extending the mutually exclusive disease categories (including a concomitant diagnosis of asthma, CB, or emphysema) to 15.

De Marco R ,et al.,[99] studied that the Incidence of chronic obstructive pulmonary disease in a cohort of young adults according to the presence of chronic cough and phlegm. To assess the incidence of COPD in a cohort of young adults and to test whether chronic cough/phlegm and dyspnea are independent predictors of COPD.An international cohort of 5,002 subjects without asthma (ages 20-44 yr) with normal lung function (FEV(1)/FVC ratio >/= 70%) from 12 countries was followed from 1991-2002 in the frame of the European Community Respiratory Health Survey II.

Incident cases of COPD were those who had an FEV(1)/FVC ratio less than 70% at the end of the follow-up, but did not report having had a doctor diagnose asthma during the follow-up. The incidence rate of COPD was 2.8 cases/1,000/yr (95% confidence interval [CI], 2.3-3.3). Chronic cough/phlegm was an independent and statistically significant predictor of COPD (incidence rate ratio [IRR], 1.85; 95% CI, 1.17-2.93) after adjusting for smoking habits and other potential confounders, whereas dyspnea was not associated with the disease (IRR = 0.98; 95% CI, 0.64-1.50). Subjects who reported chronic cough/phlegm both at baseline and at the follow-up had a nearly threefold-increased risk of developing COPD with respect to asymptomatic subjects (IRR = 2.88; 95% CI, 1.44-5.79).The incidence of COPD is substantial even in young adults. The presence of chronic cough/phlegm identifies a subgroup of subjects with a high risk of developing COPD, independently of smoking habits.

Hughes TS et al.,[100] studied that the Under estimation of mortality due to chronic obstructive pulmonary disease (COPD) Determine the frequency in which COPD is listed as a contributory cause of death, rather than the underlying cause of death, per state mortality records for a one-year period, year 2000.15,036 mortality records from Kentucky death certificates were examined for year 2000 for all deaths due to diseases most often associated with COPD; notably, heart disease, pneumonia/influenza, and asthma.Cases in which COPD was listed as a contributory cause of death for asthma, pneumonia and influenza was small (less than 1%). Cases in which COPD was listed as a contributory cause of death for heart disease was much higher at 6.8% (824 out of 12,084). Counting these cases increases the COPD age-adjusted mortality rate 39%, from 52.4 to 72.7/ 100,000 people.This study

provided evidence to generate and support the hypothesis that COPD mortality is underestimated in Kentucky when the underlying cause of death is heart disease, thus underestimating the true burden of disease. COPD is a chronic, often severe disease commonly associated with comorbid conditions such as heart disease that ultimately lead to death, but which may not be accurately reflected in mortality statistics. Accurate reporting is essential for health planning, education, research, and treatment options.

DRUG PROFILE

FLUTICASONE PROPIONATE

Brand Name:

Fluticasone Propionate may be found in some form under the following brand names:

- Cutivate
- Flonase
- Flovent HFA

INDICATION

Fluticasone propionate Inhalation Aerosol[71] is indicated for the maintenance treatment of asthma as prophylactic therapy. It is also indicated for patients requiring oral corticosteroid therapy for asthma.

CHEMICAL NAME

S-(fluoromethyl)-6α,9-difluoro-11β, 17-dihydroxy-16α-methyl-3-oxoandrosta-1, 4-diene-17β-carbothioate, 17-propionate.

CHEMICAL STRUCTURE

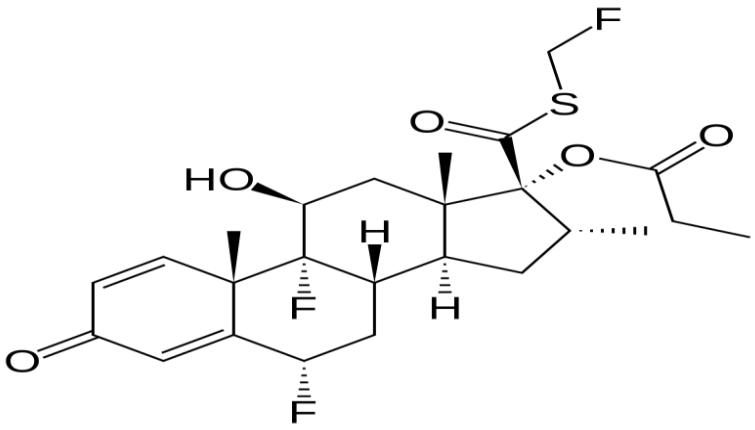

Figure: 5 Structure of fluticasone

PHARMACOLOGY

Fluticasone propionate is a highly selective agonist at the glucocorticoid receptor with negligible activity at androgen, estrogen, or mineralocorticoid receptors, thereby producing anti-inflammatory and vasoconstriction effects. It has been shown to have a wide range of inhibitory effects on multiple cell types (e.g. mast cell, eosinophil, neutrophil, macrophages, and lymphocytes) and mediators (e.g. histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation. Fluticasone propionate is stated to exert a topical effect on the lungs without significant systemic effects at usual doses, due to its low systemic bioavailability.

MECHANISM OF ACTION

Binds to the glucocorticoid receptor. Unbound corticosteroids cross the membranes of cells such as mast cells and eosinophils, binding with high affinity to glucocorticoid receptors (GR). The results include alteration of transcription and protein synthesis, a decreased release of leukocytic acid hydrolases, reduction in fibroblast proliferation, prevention of macrophage accumulation at inflamed sites, reduction of collagen deposition, interference with leukocyte adhesion to the capillary wall, reduction of capillary membrane permeability and subsequent edema, reduction of complement components, inhibition of histamine and kinin release, and interference with the formation of scar tissue.

In the management of asthma, the glucocorticoid receptor complexes down-regulates proinflammatory mediators such as interleukin-(IL)-1, 3, and 5, and up-regulates anti-inflammatory mediators such as IkappaB [inhibitory molecule for nuclear factor kappaB1], IL-10, and IL-12. The antiinflammatory actions of

corticosteroids are also thought to involve inhibition of cytosolic phospholipase A2 (through activation of lipocortin-1 (annexin)) which controls the biosynthesis of potent mediators of inflammation such as prostoglandins and leukotrienes.

PHARMACOKINETICS

The majority of the pharmacokinetic data was obtained via other routes of administration.

Absorption

Indirect calculations indicate that fluticasone propionate delivered by the intranasal route has an absolute bioavailability averaging less than 2%. Trials using oral dosing of labeled and unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone propionate is negligible (< 1%), primarily due to incomplete absorption and presystemic metabolism in the gut and liver. After intranasal treatment of patients with rhinitis for 3 weeks, fluticasone propionate plasma concentrations were above the level of detection (50 pg/mL) only when recommended doses were exceeded and then only in occasional samples at low plasma levels.

Distribution

Following intravenous administration, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averaged 4.2 L/kg.

The percentage of fluticasone propionate bound to human plasma proteins averaged 99%. Fluticasone propionate is weakly and reversibly bound to erythrocytes and is not significantly bound to human transcortin.

Elimination

Following intravenous dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. The total blood clearance of fluticasone propionate is high (average: 1,093 mL/min), with renal clearance accounting for less than 0.02% of the total.

Metabolism

The only circulating metabolite detected in man is the 17β-carboxylic acid derivative of fluticasone propionate, which is formed through the CYP3A4 pathway. This metabolite had less affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolites detected in vitro using cultured human hepatoma cells have not been detected in man.

Excretion

Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites.

PHARMACODYNAMICS

Fluticasone is an extremely potent vasoconstrictor and anti-inflammatory agent. Its effectiveness in inhaled forms is due to its direct local effect.

INDICATION AND DOSAGE

Inhalational:

The recommended adult dose of fluticasone propionate powder for oral inhalation) for the prevention of asthma symptoms is 100 to 1000 mcg of fluticasone

propionate twice daily, depending on previous treatment with corticosteroids. The recommended adult dose of fluticasone propionate aerosol for oral inhalation) for the prevention of asthma symptoms is 88 to 440 mcg of fluticasone propionate twice daily, depending on previous treatment with corticosteroids.

Topical:

The recommended adult dose of fluticasone propionate nasal spray for the treatment of allergic rhinitis symptoms is 2 sprays per nostril (for a total of 200 mcg) of fluticasone propionate every 24 hours. Once symptoms are controlled at this dose, the dose may be decreased to 1 spray per nostril (for a total dose of 100 mcg) every 24 hours.

The recommended dose of fluticasone propionate cream, lotion, and ointment for the relief of skin swelling and redness its application to the affected area once or twice daily until control is achieved.

MEDICAL USES

Asthma

Fluticasone is used by powder or aerosol inhalation for the prophylaxis of asthma. Typical initial doses in the UK range from 100 to 250 micrograms twice daily in mild asthma up to 1 mg twice daily in severe asthma, adjusted according to response. Children over four years of age may be given initial doses of 50 to 100 micrograms twice daily, increased to 200 micrograms twice daily if necessary. The drug may also be given via a nebuliser in severe chronic asthma. Usual adult doses are 0.5 to 2 mg twice daily. Children aged four to sixteen years may be given 1 mg twice daily.

Allergic rhinitis

Nasal spray preparation of fluticasone propionate is used in the prophylaxis and treatment of allergic rhinitis. The usual dose is 100 micrograms into each nostril once daily, increased if necessary to 100 micrograms into each nostril twice daily. Children aged 4-11 years may be given half these doses.

Nasal polyps

Fluticasone propionate nasal drops are used in the treatment of nasal polyps. 200 micrograms should be instilled into each nostril once or twice daily for at least four to six weeks.

Other

Creams and ointments containing 0.05% and 0.005% Fluticasone propionate, respectively, are available and applied topically in the treatment of various skin disorders. It can be given orally in the treatment of Crohn's disease and ulcerative colitis. Some benefit was also reported in coeliac disease.The dose is 5 mg four times daily but some consider higher doses necessary.

INTERACTIONS

Fluticasone propionate is broken down by CYP3A4[72] (Cytochrome P450 3A4), and has been shown to interact with strong CYP3A4 inhibitors such as ritonavir and ketoconazole.

Ritonavir is a common drug used in the treatment of HIV. Coadministration of ritonavir and fluticasone may lead to increased levels of fluticasone in the body, which may lead to Cushing's Syndrome and adrenal suppression.

Ketoconazole, an antifungal drug, has also been shown to increase fluticasone concentration leading to systemic corticosteroid side effects.

ADVERSE EFFECTS

If taken correctly, the nasal spray and oral inhaler formulation have less corticosteroid side effects than the tablet formulation because they limit systemic (blood) absorption. However, if the spray or inhaler is used at higher than recommended doses or with other corticosteroids, serious side effects can occur. These systemic corticosteroid side effects include weakened immune system, increased risk of systemic infections, osteoporosis, and elevated pressure in the eyes.

Nasal spray

Common side effects may include nasal irritation, headache, nausea, vomiting, diarrhoea, nosebleed, and cough. Rare side effects include painful white patches in nose or throat, sore throat, bruising (erythema nodosum), vision problems, swelling of face or neck, and difficulty breathing or swallowing.

Oral inhaler

Common side effects may include upper respiratory tract infection, throat irritation, thrush, cough, and headache. Rare side effects include bruising, swelling of the face/neck, depression, tiredness, and shortness of breath.

BUDESONIDE

Brand names: Rhinocort, Rhinocort Aqua, Rhinocort Allergy

INDICATION

Maintenance Treatment of Asthma budesonide inhalation suspension is indicated for the maintenance treatment of asthma and as prophylactic therapy in children 12 months to 8 years of age.

CHEMICAL NAME

16,17-(butylidenebis(oxy))-11,21-dihydroxy-, (11-β,16-α)-pregna-1,4-diene-3,20-dione[73]

CHEMICAL STRUCTURE

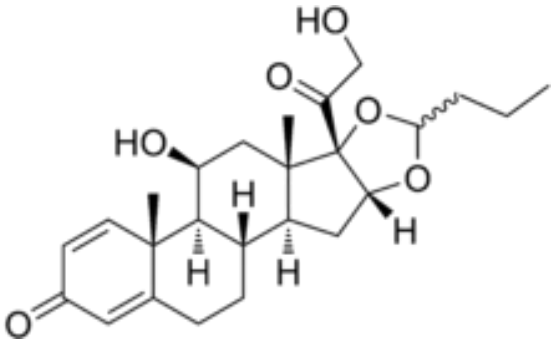

Figure :6 Structure of Budesonide

MECHANISM OF ACTION

Budesonide:

- Controls the rate of protein synthesis.
- Depresses the migration of polymorphonuclear leukocytes and fibroblasts.
- Reverses capillary permeability and lysosomal stabilization at the cellular level to prevent or control inflammation.
- Has a potent glucocorticoid activity and weak mineralocorticoid activity.

PHARMACOKINETICS

- Onset of action: Nebulization: 2-8 days; Inhalation: 24 hours
- Peak effect: Nebulization: 4-6 weeks; Inhalation: 1-2 weeks
- Distribution: 2.2-3.9 L/kg
- Protein binding: 85% to 90%
- Metabolism: Hepatic via CYP3A4 to two metabolites: 16 alpha-hydroxyprednisolone and 6 beta-hydroxybudesonide; minor activity
- Bioavailability: Limited by high first-pass effect; Capsule: 9% to 21%; Nebulization: 6%; Inhalation: 6% to 13%
- Half-life elimination: 2-3.6 hours
- Time to peak: Capsule: 0.5-10 hours (variable in Crohn's disease); Nebulization: 10-30 minutes; Inhalation: 1-2 hours; Tablet: 7.4-19.2 hours
- Excretion: Urine (60%) and feces as metabolites.

MEDICAL USES

Asthma

Budesonide[74] is nebulized for maintenance and prophylactic treatment of asthma including patients who require oral corticosteroids and those who may benefit from a systemic dose reduction.

Inflammatory bowel disease Formulations of delayed-release Budesonide can be effective treatment for mild-to-moderately active Crohn's disease involving theileum and/or ascending colon.[12] A Cochrane review found evidence for up to 3 months of maintenance of remission Crohn's disease.

Budesonide assists in the induction of remission in people with active ulcerative colitis.

SIDE-EFFECTS

Budesonide may cause:

- Nose irritation or burning
- Bleeding or sores in the nose
- Lightheadedness
- Upset stomach
- Cough
- Hoarseness
- Dry mouth
- Rash
- Sore throat
- Bad taste in mouth
- Change in mucus

In addition, the following symptoms should be reported immediately:

- Difficulty breathing or swelling of the face
- White patches in the throat, mouth, or nose
- Irregular menstrual periods
- Severe acne
- On rare occasions, behavioral changes (mostly affecting children)

INDICATION AND DOSAGE

Patients[75] should be instructed to prime budesonide inhalation powder prior to its initial use, and instructed to inhale deeply and forcefully each time the device is used.

The safety and efficacy of budesonide inhalation when administered in excess of recommended doses have not been established.

After asthma stability has been achieved, it is desirable to titrate to the lowest effective dosage to reduce the possibility of side effects. For patients who do not respond adequately to the starting dose after 1-2 weeks of therapy with budesonide inhalation powder , increasing the dose may provide additional asthma control.

Asthma

If asthma symptoms arise in the period between doses, an inhaled, short-acting beta2-agonist should be taken for immediate relief. Patients with 18 Years of Age and Older: For patients 18 years of age and older, the recommended starting dosage is 360 mcg twice daily. In some adult patients, a starting dose of 180 mcg twice daily may be adequate. The maximum dosage should not exceed 720 mcg twice daily. Patients 6 to 17 Years of Age: The recommended starting dosage is 180 mcg twice daily. In some pediatric patients, a starting dose of 360 mcg twice daily may be appropriate. The maximum dosage should not exceed 360 mcg twice daily.

BECLOMETHASONE DIPROPIONATE

Brand Name: Budez Inhaler Breemax Budecort HFA

CHEMICAL NAME

(8S,9R,10S,11S,13S,14S,16S,17R)-9-chloro-11-hydroxy-10,13,16-trimethyl-3-oxo-17-[2-(propionyloxy)acetyl]-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl propionate.[76]

CHEMICAL STRUCTURE

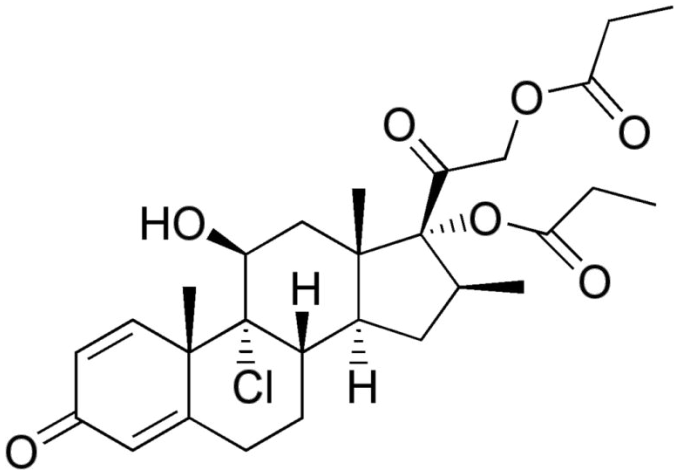

Figure :7 Structure of Beclomethasone

MECHANISM OF ACTION

Unbound corticosteroids cross cell membranes and bind with high affinity to specific cytoplasmic receptors. The result includes inhibition of leukocyte infiltration at the site of inflammation, interference in the function of mediators of inflammatory response, suppression of humoral immune responses, and reduction in edema or scar tissue. The anti-inflammatory actions of corticosteroids are thought to involve phospholipase A2 inhibitory proteins, lipocortins, which control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes. For the investigated use in the treatment of GvHD or Crohn's, beclometasone acts by binding

to interleukin-13 to inhibit cytokines, which in turn inhibits inflammatory chemicals downstream.

PHARMACOKINETICS

Absorption

Rapidly absorbed[77].

Nasal inhalation

Primarily deposited in the nasal passage; majority of the drug is eventually swallowed. Bioavailability following administration is 44% (Beconase AQ).

Oral inhalation

Systemic bioavailability from lungs is about 20%.

Distribution

87% protein bound (94% to 96% for beclomethasone 17-monoprionate).

Metabolism

Metabolized to beclomethasone 17-monopropionate (active) and free beclomethasone (very weak activity).

Elimination

Primarily excreted in feces. Less than 10% excreted in urine. The half-life is 2.8 h for beclomethasone 17-monopropionate.

Onset Within 24 h (oral inhalation). Within 3 days (nasal inhalation)

SIDE EFFECTS

Get emergency medical help if you have any of these signs of an allergic reaction: hives; difficult breathing; swelling of your face, lips, tongue, or throat.

Common side effects may include:

- headache;
- dryness in your mouth, nose, or throat after use;
- stuffy nose, sinus pain, sore throat, cough; or
- hoarseness or deepened voice.

DOSING INFORMATION

Usual Adult Dose for Asthma -- Maintenance:

40 mcg/inh and 80 mcg/inh inhalation aerosols:

2 inhalations (40 mcg each) twice a day. Alternatively, 2 inhalations (80 mcg each) twice daily has been effective in some patients who previously received inhaled steroids. Do not exceed 640 mcg a day.[78]

Comments: Improvement in asthma symptoms should be expected within the first or second week of starting treatment, but maximum benefit should not be expected until 3 to 4 weeks of therapy. For patients who do not respond adequately to the starting dose after 3 to 4 weeks of therapy, higher doses may provide additional asthma control.

Usual Pediatric Dose for Asthma -- Maintenance:

Children over 12 years of age:

40 mcg/inh and 80 mcg/inh inhalation aerosols:

1 or 2 inhalations (40 mcg each) twice a day. Or 1 inhalation (80 mcg) twice a day. Alternatively, 2 inhalations (80 mcg each) twice daily has been effective in some patients who previously received inhaled steroids. Do not exceed 640 mcg a day.

AIM AND OBJECTIVE

AIM

The aim of the study is to compare the efficacy and adverse effects of fluticasone propionate with that of budesonide and beclomethasone dipropionate in COPD patients.

OBJECTIVE

This study is designed to Evaluate the efficacy of fluticasone propionate with that of budesonide and beclomethasone dipropionate in improving lung function, decreasing symptoms and need for rescue medication in COPD

- To establish the effectiveness patient counselling
- To statistically analyze the variables in order to find out the significance

MATERIALS AND METHODOLOGY

Methods

This study was conducted in Rasiclinic, Ramanathapuram, Tamilnadu, Owned by **Dr.M.Faruk M.B.B.S.,DAC.,D.C.H.,** for a period of 16 weeks from Sep 2015 to Dec 2015. The clinic has its own spirometry testing unit. The aim of the study is to compare the efficacy and adverse effects of fluticasone propionate with that of budesonide and beclomethasone dipropionate in COPD patients.

The study design was approved by Institutional ethical committee. A written informed consent was obtained from each patient. The study was conducted in four different phases, they are as follows:

Phase 1

- Survey was conducted with the use of the inhaled corticosteroids from pharmacy outlet and hospital in Ramanathapuram study related enquires were consulted with physician **Dr.M.Faruk.**
- Literature survey was made.

Phase 2

Protocol was designed

Phase 3

As per the protocol and study requirements the patients were selected interviewed, counselled and finally included in the study.

Phase 4

Collection of the data was done from the patients visiting the clinic from the data collected results were drawn and the conclusion was made.

STUDY DESIGN

This was an open label, randomized parallel group study.

Sample size

A total of 60 patients were involved for the study and they were selected on the basis of the following criteria

Inclusion criteria:

1. Patients with the age group of 20-55 years of either sex
2. Patients with a history of episodic wheezing,difficulty in breathing, chest tightness and cough with or without expectoration
3. Patients having nocturnal symptoms and family history of COPD

Exclusion criteria:

1. Pregnant and lactating women
2. Smokers and patients with symptoms related to occupation
3. Patients who were already on steroid treatment for bronchial asthma
4. Patients with history of pulmonary tuberculosis, chronic obstructive pulmonary disease, recurrent pulmonary emboli, carcinoid tumor, tropical eosinophilia
5. Patients with history of diabetes mellitus,hypertension, chronic renal failure
6. Patients with history of bronchogenic carcinoma and suspected malignancy anywhere in the body

Source of data

Data were collected from the patients by different methods, that includes Interview with patient from case note prescriptions from the patients From the

treatment chart available and From the laboratory data which includes the pulmonary function test (PFT)

STUDY DESIGN

The total number of patients was randomized into 3 groups. Each group had 20 patients.

Group1: Fluticasone propionate inhalation therapy 100 µg twice daily.

Group2: Budesonide inhalation therapy 200 µg twice daily.

Group3: Beclomethasone dipropionate inhalation therapy 200 µg twice daily.

All the patients were advised to take Salbutamol inhalation (100 µg per puff) as needed. Metered dose inhaler with spacer (Figure 2) was used for taking medication. Patients were shown inhalation technique with spacers. They were advised to rinse their mouth after each inhalation. They were followed up once in every two weeks till a period of 12 weeks. At each visit, they were clinically assessed and pulmonary function tests were done.

Figure:8 Spacer

Method of data collection

The data was collected in a suitable case report form and the data collected includes

- Patient personal details
- Duration of COPD
- Concomitant disease
- Study medication details
- Vital sign and physical examination details
- Laboratory data such as FEV1 value
- Symptoms and Questionnaires
- Conclusion outcomes like ADR, drug interactions

All the above mentioned data were entered for each visit. The patient were reminded of their follow up visit details through telephonic messages. Review of medical chart and follow up performed on all eligible patients included in the study. This ensures close monitoring of the patients status on the basis of observational and laboratory parameters.

Clinical outcomes

The clinical outcome was assessed by different factors like the change in FEV1 value, efficacy of the therapy and symptomatic changes.

Efficacy

By means of clinical response the efficacy of the drug was assessed and the clinical response was considered to be satisfactory, if the patients signs and symptoms are reduced in each visit.

Adverse drug reaction

Clinical adverse effect data was collected from all the patients from both the groups

Patient counselling

Counselling was given to the patient regarding the disease and the realted complication, drug they use,the ideal way of using the inhalers,the need for washing the mouth after the steroid inhalation and also given nutritional counselling.

Statistical Analysis

Data of each patient was collected every 2 weeks regarding the symptom, spirometry, Drug score was collected Every 2 weeks regarding spirometry, symptom and drug score. Statistical analysis was done at the end, using values at 0 week (end of run-in period) as the baseline for comparison.Each group was analyzed for improvement after taking the respective steroid inhaler with in the group and with the other groups. Statistical analysis was done using, Two tailed P value test was applied to test the level of significance and $P<0.001$ was considered as level of significance. Data's were presented in Mean $\pm$ SEM and percentages as applicable .

OBSERVATION AND RESULTS

Table :2 AGE GROUP WISE DISTRIBUTION

S.NO	AGE GROUP (YEARS)	Fluticasone propionate	Budesonide	Beclomethasone
1	35-40	2	2	1
2	41-45	2	3	3
3	46-50	5	4	5
4	51-55	4	4	4
5	56-60	3	4	3
6	61-65	4	3	4

Out of 60 patients 5 patients were under the age group of 35 to 40, 8 patients were under the age group of 41 to 45, 14 patients were under the age group of 46 to 50, 12 patients were under the age group of 51 to 55, 10 patients were under the age group of 56 to 60, 11 patients were under the age group of 61 to 65. Patients in the age group of 46 to 50 are increasing number in this treatment.

FIGURE : 9 AGE GROUP WISE DISTRIBUTION

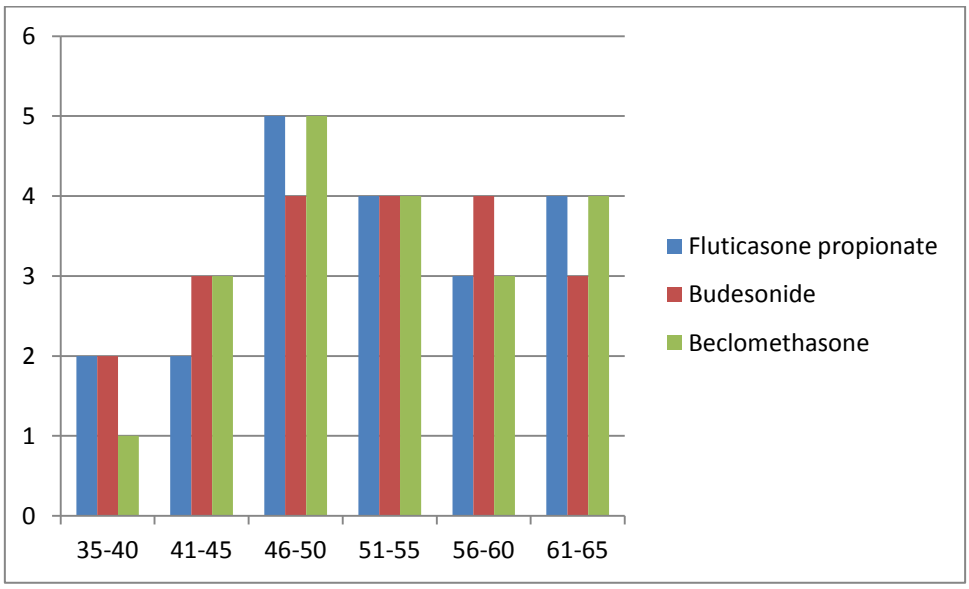

Table :3 GENDER WISE DISTRIBUTION

S.NO	Group	Female	Male
1	Fluticasone propionate	8	12
2	Budesonide	7	13
3	Beclomethasone	9	11

From the above table, Out of the 60 patients 36 (60%) were males and 24(40%) were females. This shows that male patients were mostly affected by disorders than female patients.

FIGURE : 10 GENDER WISE DISTRIBUTION

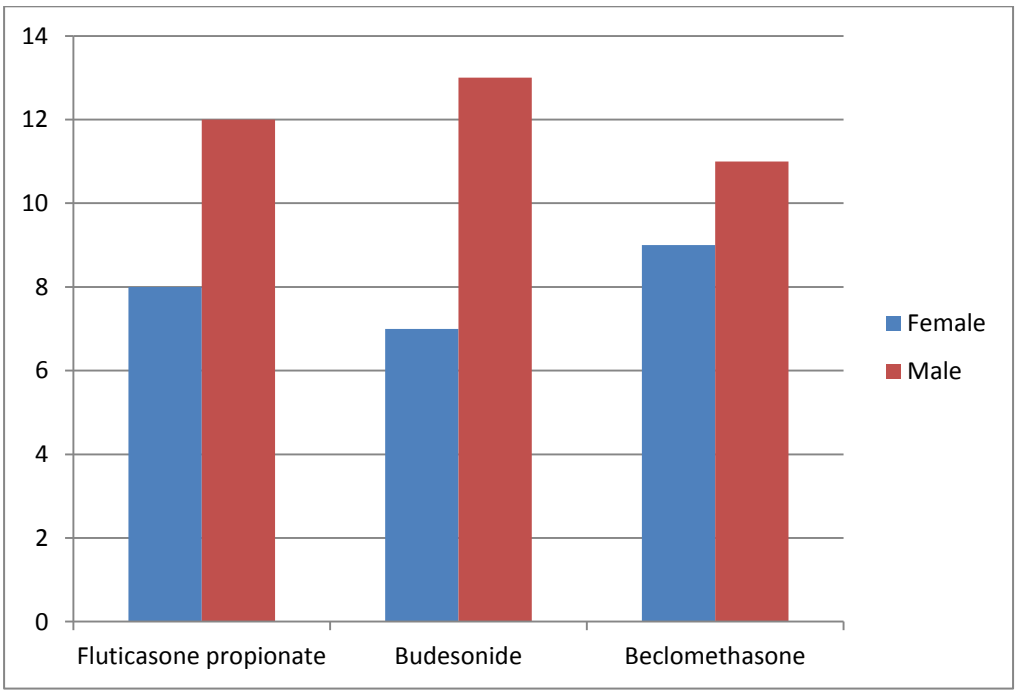

Table :4 RESIDENCE WISE DISTRIBUTION

S.NO	RESIDENCE	NUMBER OF PATIENTS	PERCENTAGE
1	Urban	36	60%
2	Rural	24	40%

From the above table, Out of the 60 patients 36 (60%) were Urban area and 24(40%) were Rural area . This shows that Urban patients were mostly affected by disorders than Rural patients due to pollution and other environmental factors.

FIGURE: 11 RESIDENCE WISE DISTRIBUTION

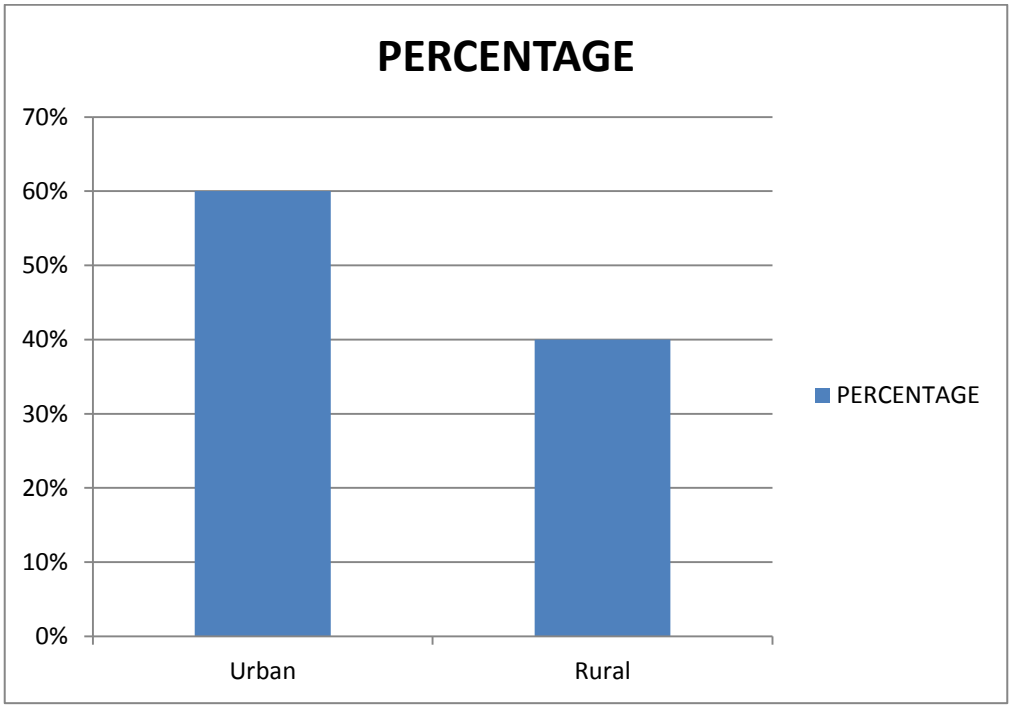

Table : 5 GROUP WISE LEVEL OF EDUCATION

S.NO	LEVEL OF EDUCATION	FLUTICASONE	BUDESONIDE	BECLOMETHASONE
1	10th or 12 th	12	13	10
2	Under Graduate	4	5	6
3	Post Graduate	4	2	4

In this study out of 60 patients 35 were 10^{th} or 12^{th} and 15 were Under Graduate, 10 were Post Graduate. so we came to know that 10^{TH} to 12^{th} qualified persons were mostly affected .

FIGURE: 12 GROUP WISE LEVEL OF EDUCATION

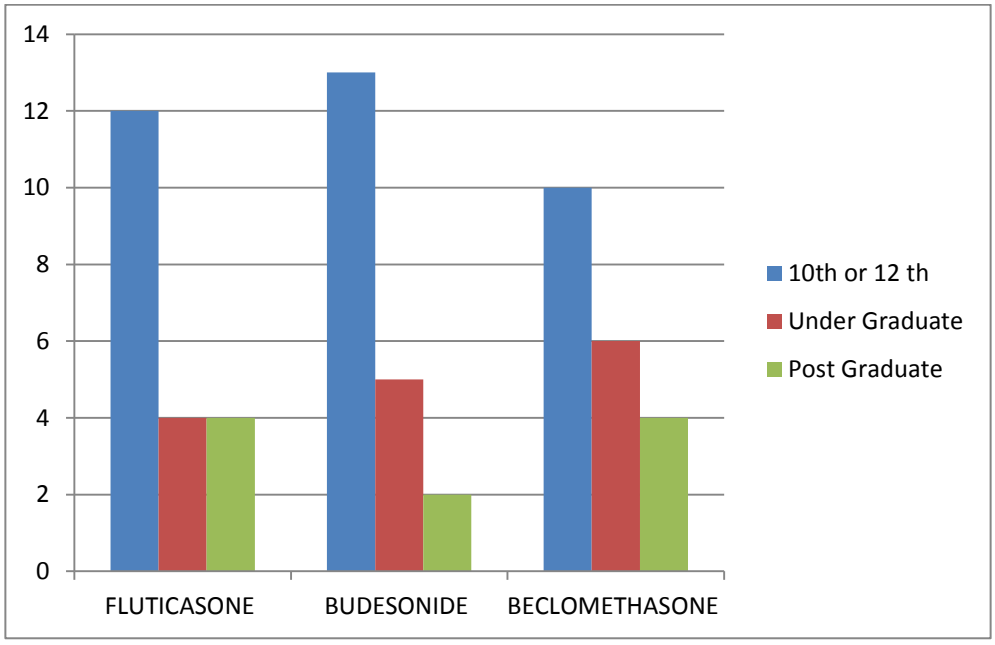

Table :6 OCCUPATION WISE DISTRIBUTION

S.NO	PATIENTS OCCUPATION	NUMBER OF PATIENTS
1	Employed	12
2	House wife	8
3	Unemployed	10

In this study out of 60 patients 12 were Employed and 8 were housewife, 10 were Unemployed. so we came to know that Employed persons were mostly affected by COPD .

FIGURE : 13 OCCUPATION WISE DISTRIBUTION

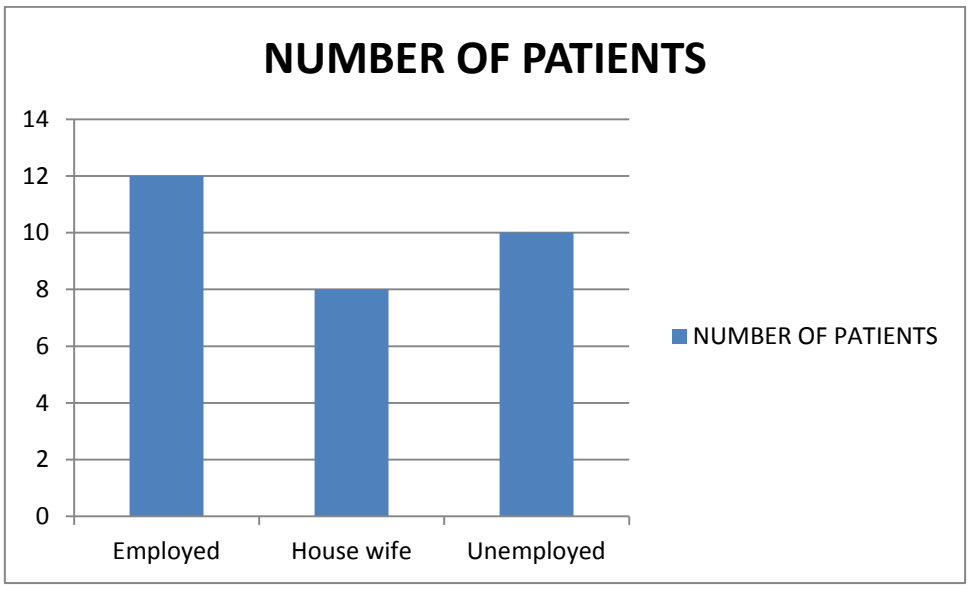

Table :7 SIGNS AND SYMPTOMS WISE DISTRIBUTION

S.NO	SIGNS AND SYMPTOMS	NUMBER OF PATIENTS KNOW	NUMBER OF PATIENTS DON'T KNOW
1	Sputum production	18	12
2	Shortness of breath	10	20
3	Productive cough	12	18
4	Wheezing	14	16
5	High pressure on the lung arteries	3	27

FIGURE :14 SIGNS AND SYMPTOMS WISE DISTRIBUTION

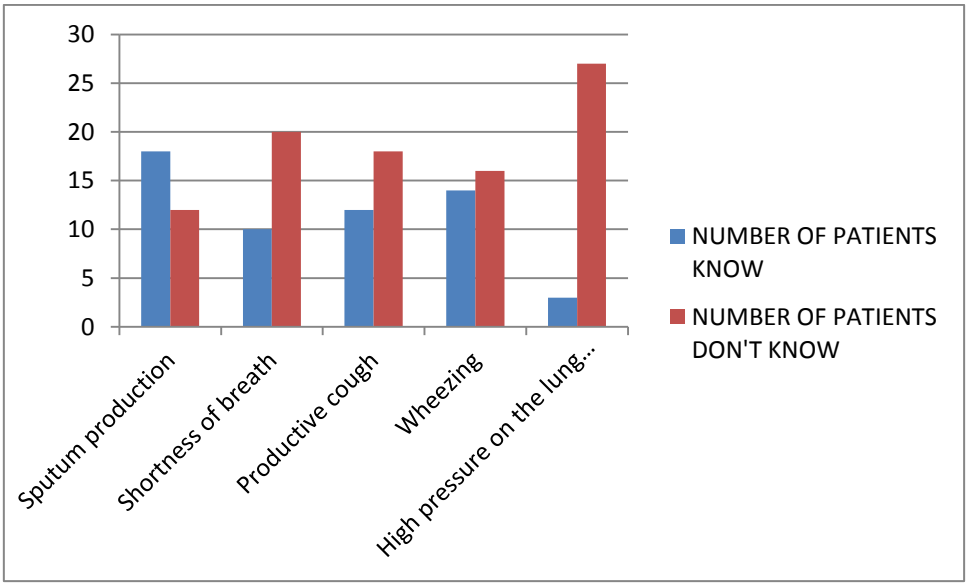

Table : 8 CAUSES WISE DISTRIBUTION

S. NO	CAUSES	NUMBER OF PATIENTS KNOW	NUMBER OF PATIENTS DON'T KNOW
1	Tobacco smoke	13	**17**
2	With occupational exposure	9	21
3	Pollution from indoor fires	12	18
4	Genetic makeup	6	24

In commonly, 30% of Patients know physical illness as the Cause for COPD, 70% of patients Don't know about physical illness as the Cause for COPD problems.

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FIGURE : 15 CAUSES WISE DISTRIBUTION

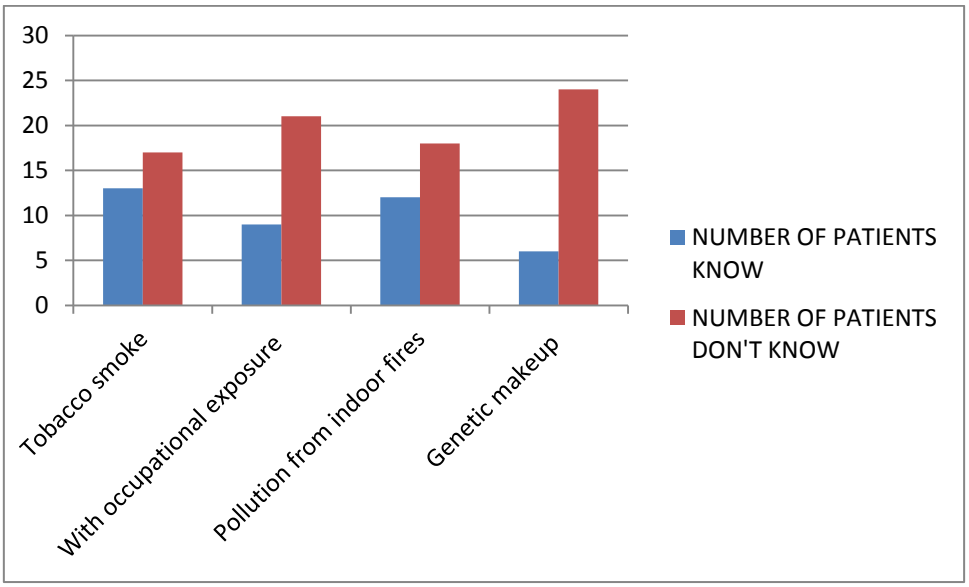


Table : 9 PREVENTION WISE DISTRIBUTION

S. NO	PREVENTION	NUMBER OF PATIENTS KNOW	NUMBER OF PATIENTS DON'T KNOW
1	Smoking cessation	13	17
2	Improving air quality	10	20
3	Occupational health	8	22
4	Influenza vaccinations	5	25
5	Pneumococcal vaccination	4	26

In commonly, 30% of Patients know Prevention for COPD eg: Smoking cessation, Improving quality, Occupational therapy, Influenza vaccinations, Pneumococcal vaccination, 70% of patients Don't know Cause Prevention for COPD eg: Smoking cessation, Improving quality, Occupational therapy, Influenza vaccinations, Pneumococcal vaccination for COPD problems

FIGURE : 16 PREVENTION WISE DISTRIBUTION

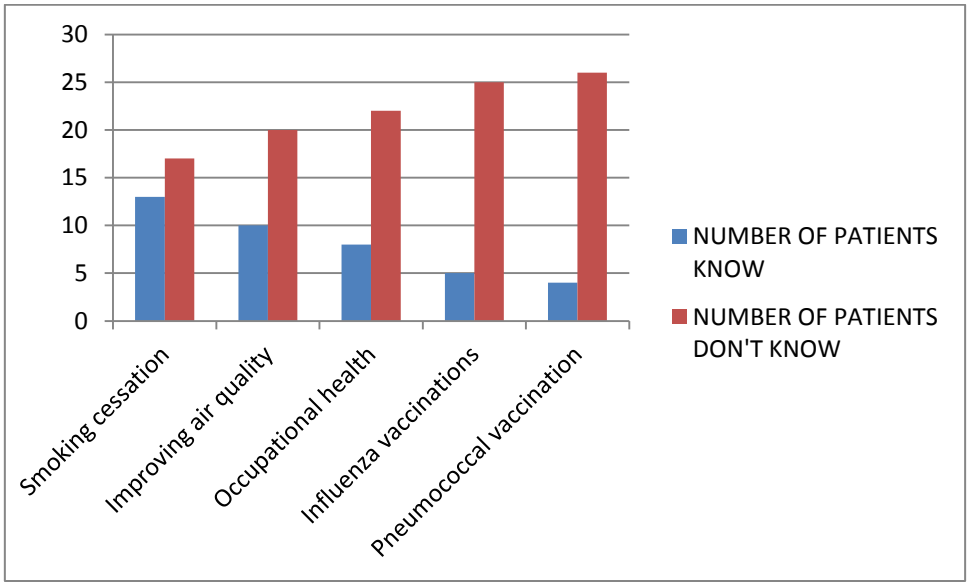


Table : 10 ASSESSMENT OF FEV1 IN FLUTICASONE GROUP

S.NO	AGE	SEX	FEV1(L)-day 1	FEV1(L)-day 120
1	39	f	2.3	2.9
2	57	m	2.1	2.7
3	46	f	2.2	2.8
4	59	f	1.9	2.5
5	36	m	3.1	3.7
6	64	m	1.9	2.5
7	46	f	2.4	3
8	41	m	2.3	2.9
9	54	f	2.2	2.8
10	63	m	2.1	2.7
11	61	f	2.1	2.7
12	54	m	2.3	2.9
13	44	f	2.6	3.2
14	62	m	2.1	2.7
15	52	m	2.5	3.1
16	48	m	2.4	3
17	53	f	2.1	2.7
18	49	m	2.6	3.2
19	47	m	2.8	3.4
20	57	m	2.1	2.7

TABLE: 11 Percentage improvement of FLUTICASONE

MEAN FEV1(L)-day 120	MEAN FEV1(L)-day 1	% IMPROVEMENT
2.9	2.3	26.08

P-value: The two tailed P value is <0.0001, considered extremely significant

T = 6.325 with 38 degrees of freedom

Mean difference = 0.6000 (Mean of column B minus Mean of column A)

Out of 60 patients, 20 (33%) were in treatment with Fluticasone Inhalation. Patients showed improvement in COPD with mean value of 26.08%.

FIGURE : 17 ASSESSMENT OF FEV1 IN FLUTICASONE GROUP

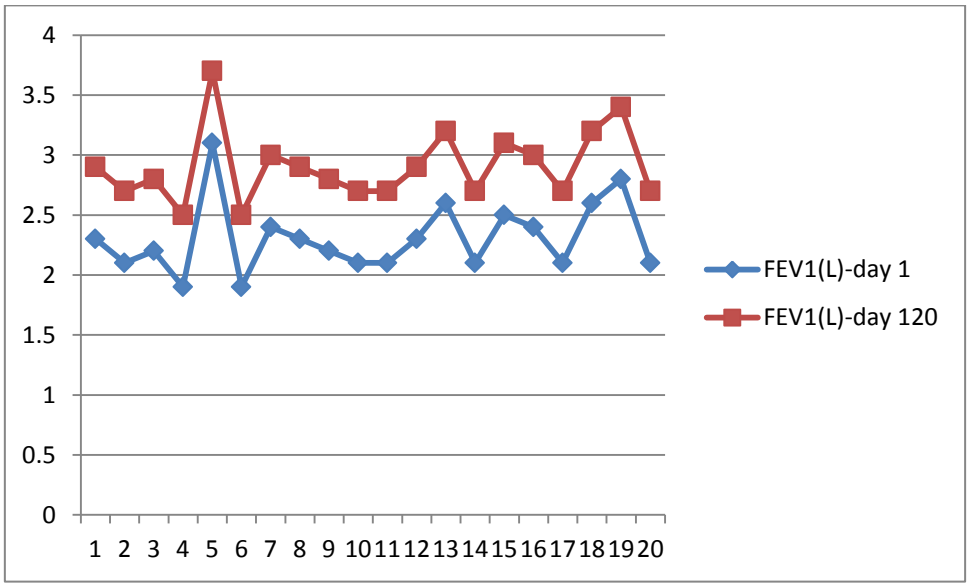


Fig: 18 Percentage improvement of FLUTICASONE

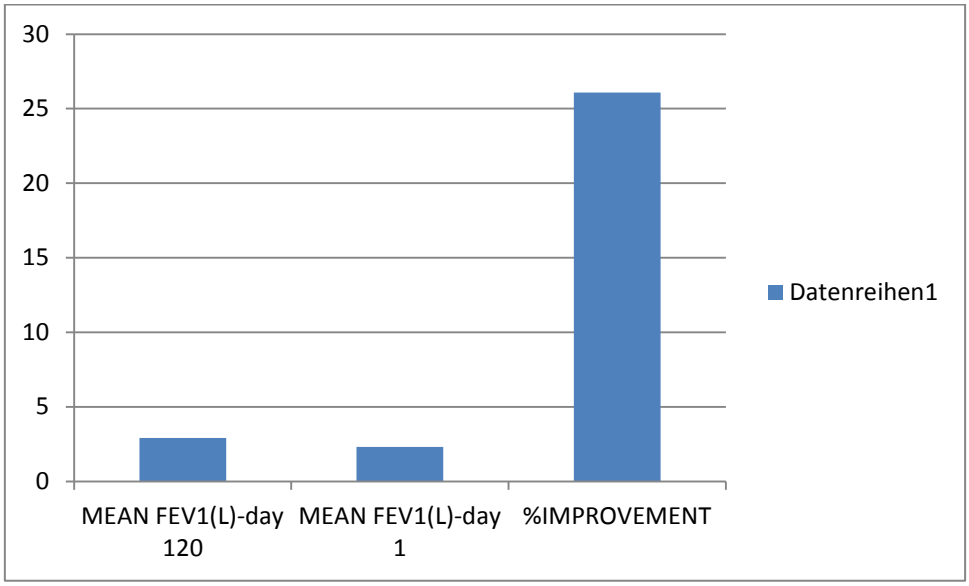


Table: 12 ASSESSMENT OF FEV1 IN BUDESONIDE GROUP

S.NO	AGE	SEX	FEV1(L)-day 1	FEV1(L)-day 120
1	38	m	2.2	2.6
2	55	m	2.2	2.5
3	48	f	2.3	2.8
4	56	f	2.1	2.5
5	38	m	3.1	3.8
6	62	m	2.1	2.6
7	45	f	2.3	2.8
8	41	m	2.4	3.1
9	52	f	2.3	2.8
10	58	m	2.2	2.6
11	63	m	1.9	2.4
12	56	m	2.1	2.4
13	42	f	2.7	3.3
14	63	m	1.9	2.5
15	55	m	2.6	2.8
16	50	m	2.8	3.2
17	51	f	2.5	2.8
18	47	m	2.7	3.2
19	49	m	2.9	3.3
20	58	f	2.3	2.7

TABLE: 13 Percentage improvement of BUDESONIDE

MEAN FEV1(L)-day 120	MEAN FEV1(L)-day 1	%IMPROVEMENT
2.83	2.38	18.9

P-value: The two tailed P value is <0.0002, considered extremely significant

T = 4.110 with 38 degrees of freedom

Mean difference = 0.4550 (Mean of column B minus Mean of column A)

Out of 60 patients, 20 (33%) were in treatment with Budesonide Inhalation. Patients showed improvement in COPD with mean value of 18.9%.

FIGURE : 19 ASSESSMENT OF FEV1 IN BUDESONIDE GROUP

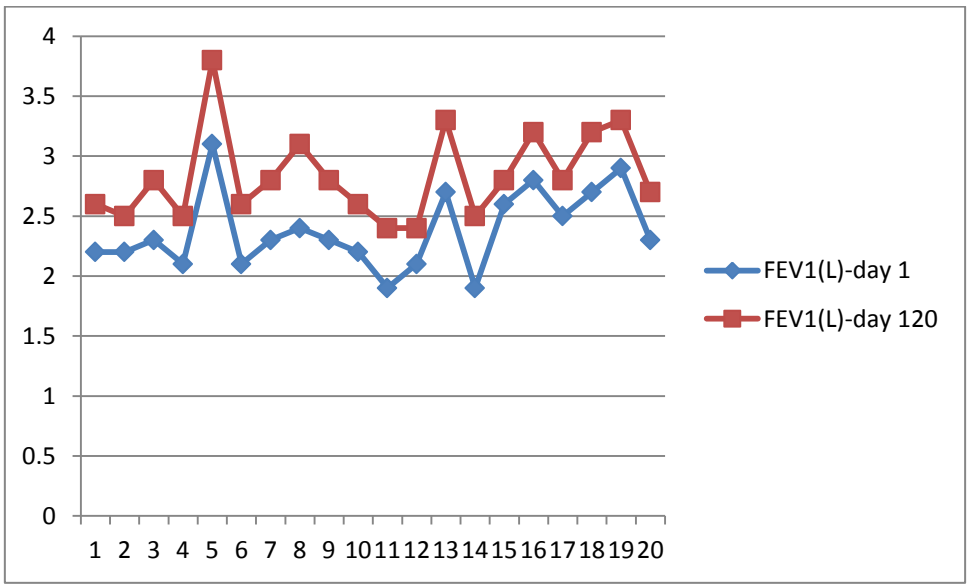


FIGURE: 20Percentage improvement of BUDESONIDE

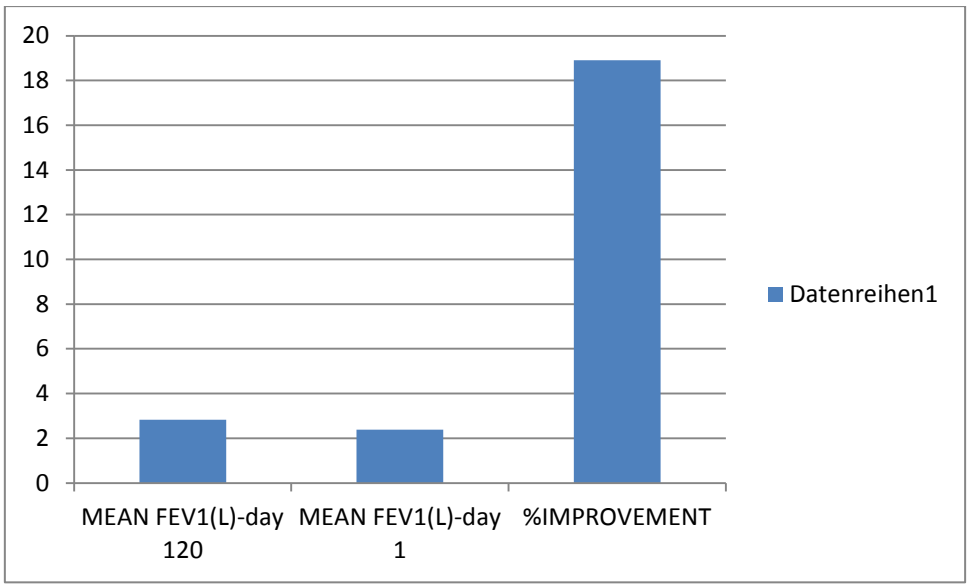


TABLE: 14 ASSESSMENT OF FEV1 IN BECLOMETHASONE GROUP

S.NO	AGE	SEX	FEV1(L)-day 1	FEV1(L)-day 120
1	39	f	2.7	2.9
2	58	m	2.1	2.4
3	48	f	2.5	2.7
4	61	m	2.1	2.6
5	54	m	2.7	3.1
6	61	m	2.2	2.6
7	48	f	2.4	2.8
8	45	f	2.7	3.1
9	52	f	2.5	2.8
10	61	m	2.6	2.9
11	57	f	2.2	2.5
12	56	m	2.5	2.8
13	48	f	2.8	3.1
14	61	m	2.4	2.6
15	53	m	2.6	2.9
16	46	m	2.6	3.1
17	54	m	2.4	2.7
18	44	f	2.3	2.8
19	42	m	2.8	3.1
20	48	f	2.3	2.6

TABLE:15 Percentage improvement of BECLOMETHASONE

MEAN FEV1(L)-day 120	MEAN FEV1(L)-day 1	% IMPROVEMENT
2.8	2.47	13.36

P-value: The two tailed P value is <0.0001, considered extremely significant

T = 4.825 with 38 degrees of freedom

Mean difference = 0.3350 (Mean of column B minus Mean of column A)

Out of 60 patients, 20 (33%) were in treatment with Beclomethasone Inhalation. Patients showed improvement in COPD with mean value of 13.36%.

FIGURE : 21 ASSESSMENT OF FEV1 IN BECLOMETHASONE GROUP

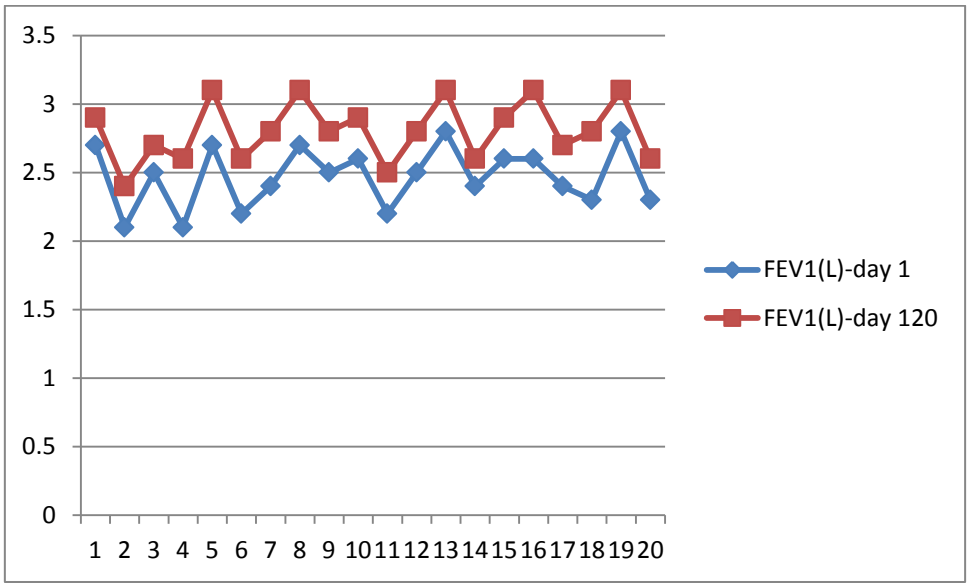


FIGURE : 22 Percentage improvement of BECLOMETHASONE

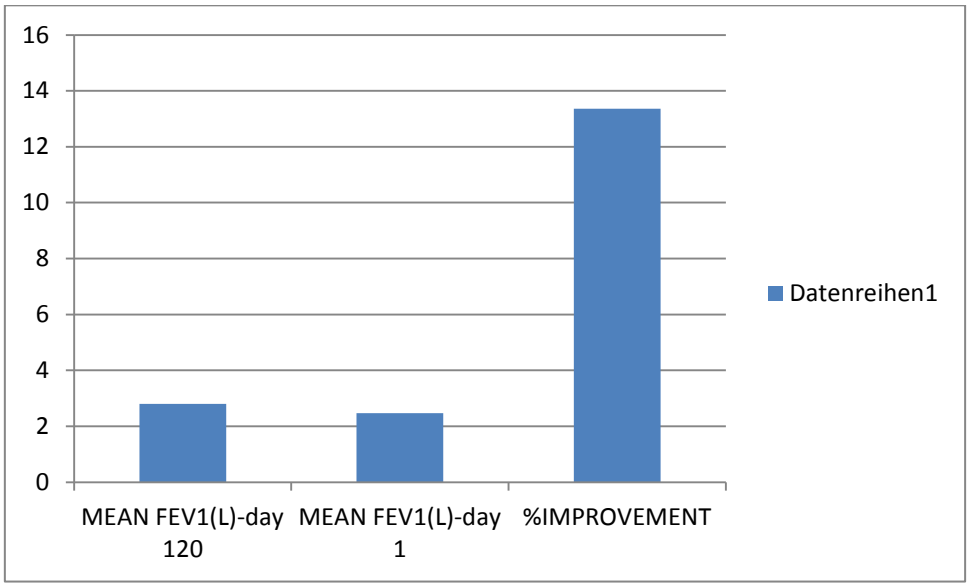


TABLE: 16 MEAN FEV1 IN FLUTICASONE, BUDESONIDE AND BECLOMETHASONE GROUP

S.NO	Group	MEAN FEV1
1	Fluticasone propionate	2.905
2	Budesonide	2.835
3	Beclomethasone	2.805

P-value: The two tailed P value is 0.0001, considered extremely significant

T = 96.139 with 2 degrees of freedom

Mean difference = 2.848 (Mean of column A minus 0.000)

The 95% confidence interval of the difference: 2.721 to 2.976

Table: 17 PERCENTAGE IMPROVEMENT IN FLUTICASONE, BUDESONIDE AND BECLOMETHASONE GROUP

S.NO	Group	%IMPROVEMENT(%FEV1)
1	Fluticasone propionate	26.08
2	Budesonide	18.9
3	Beclomethasone	13.36

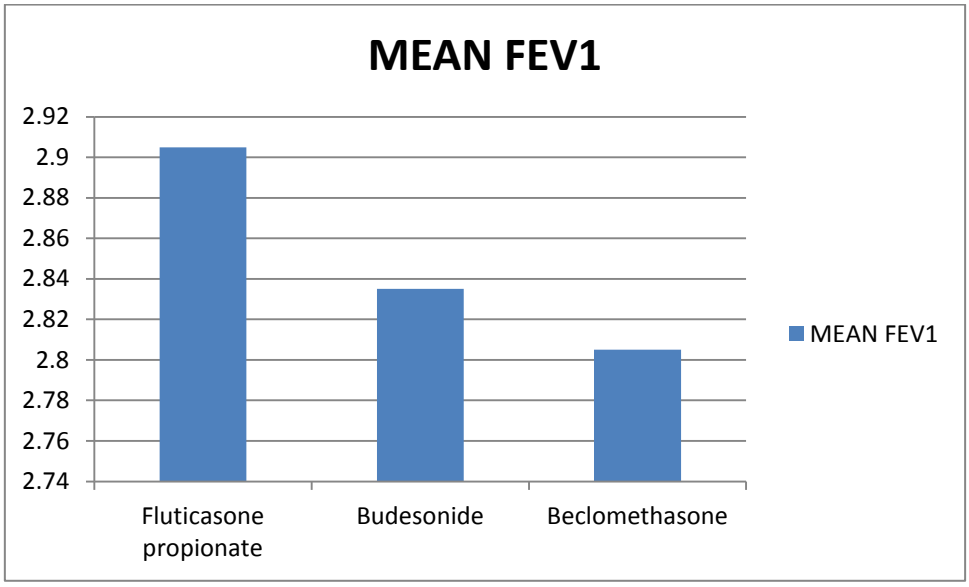
P-value: The two tailed P value is 0..340, considered significant

T = 5.281 with 2 degrees of freedom

Mean difference = 19.447 (Mean of column A minus 0.000)

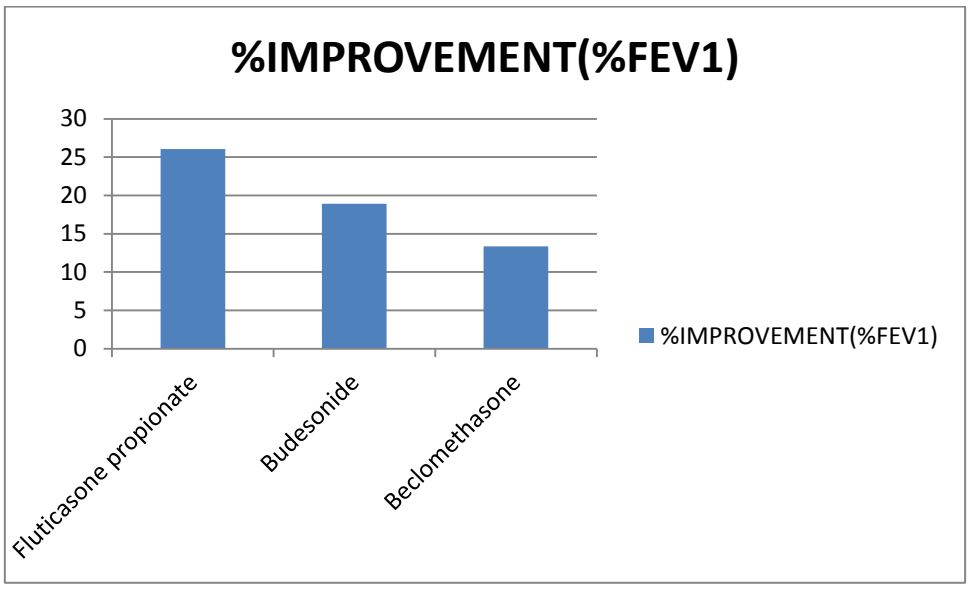
The 95% confidence interval of the difference: 3.603 to 35.291

FIGURE: 23 MEAN FEV1 IN FLUTICASONE, BUDESONIDE AND BECLOMETHASONE GROUP



Symptomatic improvement was observed in all three groups.The FEV1 improved with respect to baseline. A significant effect was observed in favour of fluticasone propionate compared with beclomethasone dipropionate and budesonide. At end point, mean FEV1 in fluticasone propionate group improved by 0.6 L compared with improvements of 0.45L in budesonide and 0.33L in beclomethasone dipropionate groups ($P < 0.001$)

FIGURE : 24 PERCENTAGE IMPROVEMENT IN FLUTICASONE, BUDESONIDE AND BECLOMETHASONE GROUP



DISCUSSION

This study I compares the efficacy of prescribed doses of inhalational steroids in COPD Patients with Fluticasone propionate 100µg twice daily, Budesonide 200 µg twice daily, Beclomethasone dipropionate 200 µg twice daily for four month period .

In the present study, the demographic characteristics of the subjects were collected. Out of the 60 COPD patients collected 60% were male and 40% were females. During the study it was observed that most of the populations were from the urban area (60%) are affected as compared to rural area (40%) and this is due to certain aggravating factors like allergens, Dust, air pollution and climatic change. It was observed that 45% of patients coming to the clinic with COPD were between the age group 35-65 years of age when compare to other age groups. Patients in the age group of 46 to 50 are increasing number in this treatment.

Out of the 60 patients 36 (60%) were males and 24(40%) were females. This shows that male patients were mostly affected by disorders than female patients. Out of the 60 patients 36 (60%) were from Urban area and 24(40%) were from Rural area . This shows that Urban patients were mostly affected by disorders than Rural patients due to pollution and other environmental factors.

In commonly, 30% of Patients know physical illness as the Cause for COPD, 70% of patients Don't know about physical illness as the Cause for COPD problems

In commonly, 30% of Patients know about prevention for COPD eg: Smoking cessation, Improving quality, Occupational therapy, Influenza vaccinations, Pneumococcal vaccination, 70% of patients Don't know about Cause Prevention for COPD.

Out of 60 patients, 20 (33%) were in treatment with Fluticasone Inhalation. Patients showed improvement in COPD with mean value of 26.08%.

Out of 60 patients, 20 (33%) were in treatment with Budesonide Inhalation. Patients showed improvement in COPD with mean value of 18.9%.Out of 60 patients, 20 (33%) were in treatment with Beclomethasone Inhalation. Patients showed improvement in COPD with mean value of 13.36%.Symptomatic improvement was observed in all the three groups. The FEV1 improved with respect to baseline.

A significant effect was observed in favour of fluticasone propionate compared with beclomethasone dipropionate and budesonide. At end point, mean FEV1 in fluticasone propionate group improved by 0.6 L compared with improvements of 0.45L in budesonide and 0.33L in beclomethasone dipropionate groups ($P < 0.001$) COPD management includes achieving and maintaining control of symptoms, maintaining lung function to normal and avoiding the adverse events from the COPD medication. Several Investigators have reported that there are significant improvements in the FEV1 values, reduction in COPD symptoms

Sailakshmi K et al., [43]compared the efficacy and adverse effect of fluticasone propionate with that of budesonide and beclomethasone dipropionate in mild persistent cases of bronchial asthma.she reported that fluticasone propionate is superior to budesonide and beclomethasone in improving lung function,decreasing symptoms and need for rescue medication in mild persistent asthma.The efficacy of the drug was studied by two methods

1. observational analysis
2. Laboratory parameters

Observational analysis is mainly concerned with the study of the occurrence of symptomatic changes upon the administration of drugs. Laboratory parameter are done to check the lung functions.

During the first visit of the patients (Day 1),the symptoms as well as the laboratory parameters(FEV1) were checked. Out of the 60 COPD patients 20 patients received Fluticasone propionate,20 patients received Budesonide and 20 patients received Beclomethasone. During the visit of the patients at (Day 120), the observational analysis and the laboratory parameters were again checked and it showed significant improvements in Fluticasone propionate treatment than budesonide and beclomethasone dipropionate.

Fluticasone propionate treatment produced significantly greater improvements in lung function (FEV1) than budesonide and beclomethasone dipropionate. No adverse effects were reported in any of the treatment groups during the study period Day time score and Nocturnal scores are improved with the patient after treatment period.

CONCLUSION

The observational analysis and the laboratory parameters were showed significant improvements in Fluticasone propionate treatment than budesonide and beclomethasone dipropionate. It can be concluded that fluticasone propionate is superior to budesonide and beclomethasone dipropionate in improving lung function, decreasing symptoms and need for rescue medication in COPD. Patient compliance was good with all the three drugs and there is no adverse effect. All the three drugs are well tolerated at doses used in this study.

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APPENDIX I

PROFORMA

Name :

Age : **Gender** | **M** | **F** |

Height : **Weight** :

Date :

Population : ☐ Rural ☐ Urban

Smoking Status : ☐ Smoker ☐ Non-Smoker ☐ Ex-Smoker

Symptoms : ☐ Breathing difficulty ☐ Chest tightness ☐ Sputum production ☐ Troubled sleep ☐ Wheezing ☐ Others

Risk : ☐ Air froid ☐ Air pollution ☐ Pollen ☐ Animals ☐ Chemicals ☐ Others. ☐ Cold air ☐ Dust ☐ Hot air ☐ Humidity ☐ Smoke

Specify…….

Concomitant disease : ☐ HTN ☐ DM ☐ HTN & DM ☐ Disease free ☐ Others.

Specify…….

Day visit Date:

Spirometry report		**FEV_1**
		PEF

Severity of disease		**Mild intermittent**
		Mild persistent
		Moderate
		Severe

DAY TIME SYMPTOM SCORE QUESTIONNAIRE

1. **How often do you experience COPD symptoms in the last week?**

0	1	2	3
Never	Few days	Several days	Every day

2. **How much did your COPD symptoms bother you over the last week?**

0	1	2	3
Not bothered	Not much bothered	Very much bothered	Severe bothered

3. **How often did your COPD symptoms affect your activities over the last week?**

0	1	2	3
Not bothered	Not much bothered	Very much bothered	Severe bothered

NOCTURNAL SYMPTOM SCORE QUESTIONNAIRE

1. **How often do you wake up with COPD symptoms during the night in the last week?**

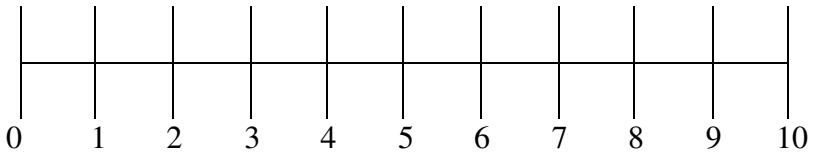
0	1	2	3
Never	Few nights	Several nights	Every nights

2. **How severe were your night symptoms in the last week?**

0	1	2	3
No symptoms	Mild	Moderate	Severe

This questionnaire will help us find out what you understand about your COPD and the treatments and support available. For each question please circle the number on the scale to show your understanding, confidence or use with each topic. If there are topics you do not know much about, feel less confident with or don't use often, then you should circle a low score. If there are topics you know more about, feel more confident with or use often then you should circle a higher score.

Example:



You should complete the questionnaire independently. If there are any questions you have difficulty answering then please ask for help. Please answer all the questions in Section A. Please complete Section B if you have attended a pulmonary rehabilitation programme. The questionnaire should take about 10 minutes to complete.

SECTION A

ABOUT COPD

1. How well do you understand what COPD is?

No understanding 0 1 2 3 4 5 6 7 8 9 10 Full understanding

2. How well do you understand how COPD changes over time?

No understanding 0 1 2 3 4 5 6 7 8 9 10 Full understanding

3. How confident are you that you can recognise an exacerbation (a significant worsening of your usual symptoms)?

Not confident 0 1 2 3 4 5 6 7 8 9 10 Very confident

4. How confident are you that you know how to alter your therapy during an exacerbation (a significant worsening of your usual symptoms)?

Not confident 0 1 2 3 4 5 6 7 8 9 10 Very confident

5. How confident are you that you know when to seek help during an exacerbation (a significant worsening of your usual symptoms)?

Not confident 0 1 2 3 4 5 6 7 8 9 10 Very confident

6. How confident are you that you know **how** to use your COPD medication (e.g. inhaler, nebuliser, and tablets)?

Not confident 0 1 2 3 4 5 6 7 8 9 10 Very confident

7. How confident are you that you know **why** you use your COPD medication?

Not confident 0 1 2 3 4 5 6 7 8 9 10 Very confident

MANAGING SYMPTOMS OF COPD

8. How often do you use breathing techniques to manage your symptoms (e.g. slowing your breathing down and pursed lip breathing)?

Never 0 1 2 3 4 5 6 7 8 9 10Always

9. How often do you pace yourself to conserve energy (e.g. plan activities, alternate light and heavy tasks)?

Never 0 1 2 3 4 5 6 7 8 9 10Always

10. How often do you use positions of ease (e.g. body positions to reduce shortness of breath)?

Never 0 1 2 3 4 5 6 7 8 9 10Always

11. How well do you understand the benefits of exercise?

No understanding 0 1 2 3 4 5 6 7 8 9 10 Full understanding

12. How confident are you that you can take part in exercise?

Not confident 0 1 2 3 4 5 6 7 8 9 10 Very confident

13. How confident are you that you can manage the low mood or depression sometimes associated with COPD?

Not confident 0 1 2 3 4 5 6 7 8 9 10 Very confident

14. How confident are you that you can manage the anxiety and panic sometimes associated with COPD?

Not confident 0 1 2 3 4 5 6 7 8 9 10 Very confident

ACCESSING HELP AND SUPPORT

15. How confident are you that you know how to get aids and appliances if you need them (e.g. shoe horn, shower seat)?

Not confident 0 1 2 3 4 5 6 7 8 9 10 Very confident

16. How confident are you that you know how to get information about welfare and benefits that you might be entitled to?

Not confident 0 1 2 3 4 5 6 7 8 9 10 Very confident

17. How confident are you that you know how to access facilities for exercise (e.g. gym, pool, walking clubs)?

Not confident 0 1 2 3 4 5 6 7 8 9 10 Very confident

18. How confident are you that you know how to get information about local support groups for people with respiratory conditions?

Not confident 0 1 2 3 4 5 6 7 8 9 10 Very confident

SECTION B

Complete this section after you have attended pulmonary rehabilitation. For each question please **circle the number** on the scale to show your views and satisfaction with each topic.

1. How satisfied were you with the amount of practical information used in the education sessions (e.g. demonstrations and practice)?

Not satisfied 0 1 2 3 4 5 6 7 8 9 10 Very satisfied

2. How satisfied were you with the content of the education sessions?

Not satisfied 0 1 2 3 4 5 6 7 8 9 10 Very satisfied

3. How satisfied were you with the content of the written materials given?

Not satisfied 0 1 2 3 4 5 6 7 8 9 10 Very satisfied

4. How approachable was/were the healthcare professional(s) who delivered the education sessions?

Not approachable 0 1 2 3 4 5 6 7 8 9 10 Very approachable

5. How accessible was the location of the education sessions (e.g. distance to walk, car parking facilities)?

Not accessible 0 1 2 3 4 5 6 7 8 9 10 Very accessible

6. Are there any topics that were not covered in the education sessions that you think should be covered?

   No Yes

   If 'yes', please insert suggested topic(s) _____

   If you would like to add any further comments please insert these in the box below.